



# Interactions of Anti-Inflammatory and Antibiotic Drugs at Mineral Surfaces Can Control Environmental Fate and Transport

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**Interactions of anti-inflammatory and antibiotic drugs at mineral  
surfaces can control environmental fate and transport**

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## Abstract

Various pharmaceutical compounds often coexist in contaminated soils, yet little is known about how their interactions impact their mobility. We here show that two typical antibiotic and anti-inflammatory agents (nalidixic acid (NA) and niflumic acid (NFA)) commonly form dimers at several representative soil- and sediment-building minerals of contrasting composition and structure. Co-binding occurs in the form of a NFA-NA dimer stabilized by hydrogen bonding and van der Waals interactions. Using dynamic column experiments containing goethite-coated sand, we then demonstrated that pre-sorbed NA effectively captured the otherwise weakly-binding NFA from solution. Simultaneously injecting NA and NFA to pre-sorbed NA enhanced even further both NA and NFA loadings, thereby altering their transport under flow-through conditions. We also showed that environmental level amounts of natural organic matter can reduce the overall retention in column experiments, yet it does not suppress dimer formation. These environmentally relevant scenarios can be predicted using a new transport model that accounts for kinetics and co-binding reactions of NFA onto NA bound to goethite through metal bonded, hydrogen-bonded and an outer-sphere complexes. These findings have important implications on assessing the fate of co-existing pharmaceutical compounds under dynamic flow conditions in contaminated soils.

**Keywords:** pharmaceutical compounds; mobility; cooperative binding; transport; modeling.

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## **Synopsis**

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61     This work contributes to efforts aiming to accurately assess co-binding mechanisms

62                     and the fate of co-existing contaminants in the environment.

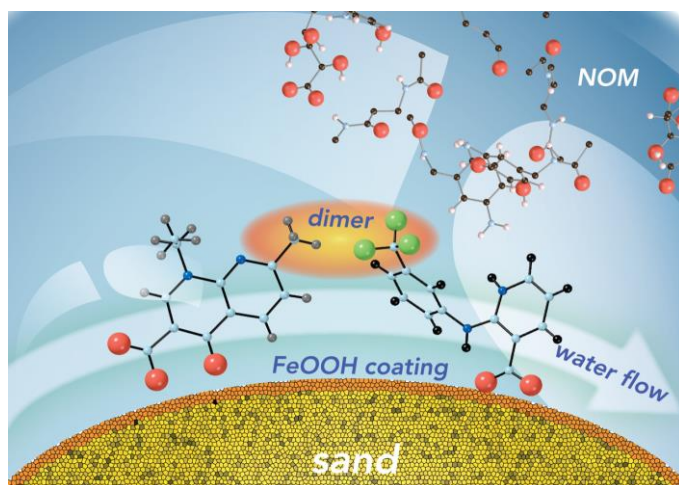
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## Graphical Abstract



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## 1. Introduction

Pharmaceutical and personal care products often co-exist in aquatic systems at levels as high as several hundred ng per L<sup>1-4</sup>. Recently, antibacterial and anti-inflammatory agents have emerged as aqueous micropollutants in surface waters, groundwaters and soils<sup>2,5</sup>. The transport and mobility of these emerging contaminants in the environment are strongly related to the nature and relative abundance of the mineral phases (*e.g.* metal oxides and clays) commonly found in the Earth's near-surface environment<sup>6-8</sup>. For this reason, several studies have focused on interactions of organic compounds with metal-oxyhydroxides and clays<sup>8-12</sup>. Still, much remains to be learned on their fate and transport mechanisms in oxide-rich environments, and particularly in multicomponent systems. In such systems, adsorption, through competitive or synergistic interactions at mineral surfaces, is key to determine the fate of pollutant mixtures<sup>13-15</sup>.

Recent spectroscopic, chromatographic and theoretical investigations have improved the description of quinolones and fluoroquinolones adsorption to Fe-oxides by identifying ligands that are (i) metal-bonded (MB; inner-sphere (IS)), (ii) hydrogen-bonded (HB; direct H-bond to surface (hydr)oxo group) or (iii) bound as outer-sphere (OS; separated by at least one hydration sheath) species. The relative importance of these species is affected by pH, ionic strength, as well as mineral surface and ligand structures<sup>16-19</sup>. More particularly, we have shown that the spatial

disposition functional groups of niflumic acid (NFA, a non-steroidal anti-inflammatory) favor HB over MB species at goethite ( $\alpha$ -FeOOH) surfaces over a broad range of pH values<sup>18,19</sup>. In contrast, the keto group and carboxylate groups of nalidixic acid (NA, a quinolone antibiotic) favor MB species.<sup>19,20</sup> Here, MB species dominate under acidic conditions, while HB/OS coexists under circumneutral to alkaline conditions.

Because most traditional environmental models are based on a single/individual contaminant basis, little is known on their transport in mixture contaminant systems, and underlying reaction mechanisms remain elusive. In addition, much of the knowledge that currently exists concerns the reactivity of environmental mineral surfaces in suspensions or slurry systems, and under equilibrium conditions<sup>7,10,21–23</sup>. Fewer investigations have been performed on the impact of water flow on the interfacial processes, and much less in flow-through system where non-equilibrium prevails. Moreover, non-equilibrium sorption under dynamic flow conditions is particularly relevant when competitive or cooperative process in presence or absence of natural organic matter (NOM) concurrently impact the mobility of target compounds<sup>4,24,25</sup>.

In this work, we assessed the ability of NA and NFA to co-bind at minerals surfaces. To identify the mineralogical controls on NA and NFA co-binding we monitored their uptake by batch adsorption on seven nanominerals of contrasting

composition and structure (goethite, magnetite, hematite, gibbsite, kaolinite, bentonite and titanium dioxide). These natural constituents of soils and sediments are the most reactive minerals in the environment, and play an important role in controlling the fate, mobility and toxicity of contaminants. Then, to emulate contaminant migration in natural environments, such as in aquifers and sediments, we monitored NA and NFA transport in column experiments using goethite-coated quartz sand particles. Goethite, a widespread mineral in aquatic and terrestrial systems, is one of the most thermodynamically stable iron oxide with a high surface area<sup>26</sup>. Furthermore, goethite is often forming coatings on less soluble soil particles such as silica sand, and thus goethite-coated sand material is generally used as a structurally stable and hydraulically conductive porous medium to mimic natural mineral assemblages<sup>27,28</sup>.

We compared NA and NFA binding (1) in isolated vs. mixed systems, and (2) in settings emulating stagnant vs. flowing groundwater containing Leonardite humic acid (LHA), a representative NOM. The NOM concentration range (5-10 mg/L) corresponds to the dissolved organic carbon typical of shallow groundwater, soil pore waters and surface waters<sup>29,30</sup>. Breakthrough curves (BTCs) of NA and NFA determined under different water velocities and residence times showed that co-binding of NA/NFA significantly altered the mobility of each compound. Although we have used an inflow concentration of NA or NFA higher than the level amounts of pharmaceuticals commonly detected in environmental systems (several hundred of ng per L)<sup>1-4</sup>, previous experimental and computational quantum findings showed that the formation of NFA-NA dimer at the surface of  $\text{AlO}(\text{OH})$  or  $\text{FeO}(\text{OH})$ , is



thermodynamically favorable, and can even occur for the very low concentration range<sup>19</sup>. In addition, dynamic breakthrough experiments provide a high solid-to-liquid ratio, *i.e.* a small volume flowing through the porous media in packed bed columns, and therefore a total contaminant loading more representative of environmental settings<sup>17,18</sup>.

Multisite complexation model (MUSIC) was also established to describe the co-binding results of NA and NFA onto goethite, and predictions of BTC have been developed from surface complexation modeling parameters combined with a new kinetics term. This chemical kinetic/transport coupling was required to accurately describe the mobility of NA and NFA in the different scenarios considered in this study. These efforts helped identify conditions under which drug co-binding is likely to prevail in the environment, and highlight the importance of coupled flow and water chemistry in controlling the mobility of pharmaceutical compounds in complex environmental media.

## 2. Materials and Methods

### 2.1 Chemicals

Nalidixic acid (NA), Niflumic acid (NFA), ferric nitrate nonahydrate ( $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ ), sodium chloride (NaCl), sodium hydroxide (NaOH), hydrochloric acid (HCl) and potassium bromide (KBr) were provided by Sigma Aldrich and were of analytical grade or better, and used without further purification. All solutions were prepared with ultrapure water. Leonardite Humic Acid Standard (1S104H) was

purchased from the International Humic Substance Society. A LHA stock solution (2 g/L, 1276 mg C/L) was prepared by dissolving 2 g LHA in 100 mL of 1 M NaOH, then diluted to 1 L with ultrapure water. Fontainebleau quartz sand (150-300  $\mu\text{m}$ ) was purchased from VWR Prolabo (France). Ultrapure water was used in all experiments.

## 2.2 Synthesis and characterization of minerals

Goethite, hematite, magnetite, gibbsite were synthesized using published methods, and described in the SI. Commercial  $\text{TiO}_2$  Millennium PC-500 (> 99% of anatase), Georgia kaolinite (KGa-1) and Bentonite (Na-montmorillonite) were used as received. More information about synthesis and characterization are given in the Supporting information (SI).

Goethite coated sand (GCS) was obtained by mixing 500 g of Fontainebleau sand with an excess of goethite ( $\sim 10$  g) in 1L of 10 mM NaCl solution. Before coating, the quartz sand was cleaned with HCl, then with  $\text{H}_2\text{O}_2$ , and rinsed with pure water. The resulting goethite-sand suspension was adjusted to pH 5 and then shaken for 24 h. After that, the coated sand was washed with ultrapure water until the runoff was clear, and then it was dried in oven at  $60^\circ\text{C}$  for 24 h. The final GCS was stored at ambient temperature. Acid digestion followed by measurements of total dissolved iron using Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP/AES), has permitted to determine the coating degree. For GCS, we found 0.9 g goethite per 100 g of coated sand. Previous studies from our group<sup>17,20</sup> confirmed that the coating

procedure did not alter the reactivity of goethite particles.

The possible dissolution of the used quartz sand was also checked in sand suspensions with two solid loadings, 1 or 10 g/L, aged for one month and at various equilibrium pH (4-10), in pure water or 0.01 M NaCl. In both cases were dissolved silicate concentrations below the detection limits of the molybdenum blue spectrophotometric method (detection limit 1  $\mu$ M) and of ICP/AES analyses (detection limit 0.2  $\mu$ M)).

### **2.3 Batch experiments**

Batch adsorption experiments were conducted in 10 mL suspensions of minerals in polypropylene tubes at a wide range of pH and in 10 mM NaCl to assess the NA/NFA co-binding on different types of minerals. The investigated pH range was adapted for each mineral to avoid mineral dissolution at very low or high pH values. All experiments were carried out under an atmosphere of N<sub>2</sub>(g) in order to avoid contributions from dissolved CO<sub>2</sub>. Suspensions were mixed for a period of 24 h by end-over-end shaking, which is largely sufficient to reach equilibrium based on preliminary kinetic study<sup>18</sup>. Aliquots of the resulting suspensions were thereafter sampled and filtered (0.2  $\mu$ m) for analysis. NA and NFA co-binding to goethite were also investigated at pH 5  $\pm$  0.1 in presence of various LHA concentrations. All batch adsorption experiments were performed in triplicates, with a reproducibility of 5 % for NA and 7 % for NFA. Results for the LHA-free systems are in the SI only.

NA and NFA concentrations in the aqueous solution were determined using a high performance liquid chromatography (HPLC) system. This was equipped with an auto sampler (Waters 717 plus) using a C18 column (250 mm×4.6 mm i.d., 5 µm), and a UV detector operating at 258 nm and 283 nm (Waters UV). The mobile phase was a mixture of water/acetonitrile (60:40 v/v) containing 0.1% of formic acid. The flow rate of the mobile phase was set at 1 mL/min in isocratic mode.

## **2.4 Continuous flow experiments**

Breakthrough column experiments were conducted in a glass chromatographic column (1.6 cm internal diameter). The porous bed had a length of 4.9 cm and a dry mass of 15 g. After packing to a uniform bulk density (1.52 g/cm<sup>3</sup>), the column was wetted upward with a background electrolyte solution (NaCl, 10 mM) at a constant flow rate for at least 24 h until the column was saturated and each parameter (pH, conductivity) became constant. After water saturation, 1 pore volume of 10 mM KBr (with 10 mM NaCl, pH 5) was injected in between the NaCl background solution to determine the flow characteristics of the porous bed. The tracer BTC was recorded by ion chromatography (Fig. S1 in supporting information, SI). The classical convection dispersion equation (CDE) was applied to describe the 1D transport of a non-reactive solute under steady-state water flow in a saturated column (*cf.* SI for detailed description of model). The fitting parameters of the bromide elution confirmed the flow homogeneity and predominance of a convective regime in the column. The mass balance ratios calculated based on BTCs of Br<sup>-</sup> were close to 100% (Fig.

S1). The hydrodynamic parameters estimated includes total water content  $\theta$  ( $0.36 \pm 0.005$ ) and dispersivity  $\lambda$  ( $242 \pm 2 \mu\text{m}$ ) (See SI).

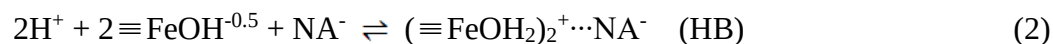
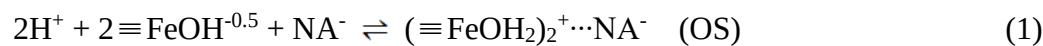
After the pulse tracer experiments, four sets of column experiments were performed by step-injection at the same constant flow rate of : (i) NFA/(NA+NFA): injection of  $10 \mu\text{M}$  of NFA first, then  $10 \mu\text{M}$  NA+ $10 \mu\text{M}$  NFA when the total breakthrough of NFA was achieved; (ii) NA/(NA+NFA): injection of  $10 \mu\text{M}$  of NA first, then  $10 \mu\text{M}$  NA+ $10 \mu\text{M}$  NFA when the total breakthrough of NA was achieved, (iii) (NA+NFA): simultaneous injection of  $10 \mu\text{M}$  NA+ $10 \mu\text{M}$  NFA directly; (iv) (NA+NFA+LHA): simultaneous injection of  $10 \mu\text{M}$  NA+ $10 \mu\text{M}$  NFA +  $5/10 \text{ mg/L}$  LHA. In all four approaches, influent solutions were prepared at  $\text{pH}_{\text{in}} 5 \pm 0.1$  and contained  $10 \text{ mM}$  of NaCl. Continuous on-line pH measurement was performed using pre-calibrated pH flow through sensor. In addition, the pH of collected fractions was often checked using a pH-meter (HI2210, HANNA®). The breakthrough curves (BTCs) were expressed as the relative aqueous concentration of solute against the number of pore volumes ( $V/V_p$ ), where  $V_p$  represents the pore volume of column. The adsorbed amounts of NA and NFA were determined by integrating the area above the entire breakthrough curve of each compound, as previously reported<sup>28,31</sup>. The mass balance was further confirmed by carrying out solid-phase extraction on GCS, as described in previous work<sup>32</sup>. Briefly, the solid from packed column was transferred into an aqueous solution and then pH was adjusted to 11, and the suspension was stirred for 1h. The average extraction recovery derived from several desorption tests

246 lied at  $97.9 \pm 3.5\%$ , confirming that only adsorption took place in the GCS column,  
247 and that molecule breakdown by, for example, oxidation, did not occur under the  
248 experimental conditions of this study. The aqueous concentrations of NA and/or NFA  
249 in the outflow were determined by HPLC. In all the column experiments, the leaching  
250 iron from GCS column was negligible. All experiments were conducted in duplicates,  
251 and the estimated error lied at 5% for NA and NFA.

## 253 **2.5. Surface complexation modeling combined with kinetics**

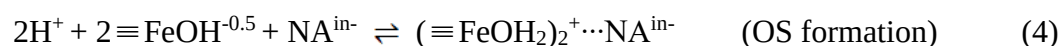
254 A surface complexation model (SCM) was used to predict adsorption under  
255 equilibrium condition. However, non-equilibrium may predominate in the dynamic  
256 column experiments, and thus implementation of kinetics in surface complexation  
257 reactions is crucial to accurately describe the mobility behavior. It was reported that a  
258 fast formation of outer sphere complexes is a prerequisite for inner sphere (IS)  
259 complexes formation, which is a rate-limiting process<sup>33,34</sup>. According to a previous  
260 spectroscopic study<sup>34</sup> showing that the conversion of hydrogen-bonded organic  
261 species to MB complexes was time-dependent, HB and OS complexes can be  
262 considered as intermediate species in our proposed conceptual model. To integrate  
263 kinetics in our SCM, we assume surface complexation reactions occur in two steps: (i)  
264 formation of precursor surface species (fast intermediate step) and (ii) formation of  
265 final surface species (rate-limiting step). According to our previous spectroscopic and  
266 theoretical investigations<sup>18,19</sup>, NA can form (i) MB surface complexes *via* a NA keto  
267 group and one oxygen of the carboxylate group, (ii) HB complexes (surface

hydration-shared ion pair) and (iii) OS complexes (solvent-surface hydration-separated ion pair, where NA keeps its first hydration sphere) as follows:



All modeling parameters are provided in Table S2.

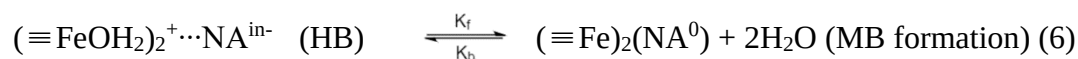
To distinguish the two-step reactions in PHREEQC-2, we have applied the previously published approach<sup>35</sup>. Briefly, we defined one intermediate ('in') 'NA<sup>in</sup>' and one equilibrium 'NA' species. Here, 'NA<sup>in</sup>' is an intermediate complex first in the form of a OS species:



This OS species then converts to a HB species:



This conversion is a fast process, whereas the resulting HB species converts to a MB species through the following rate-limiting process:



Here,  $k_f$  and  $k_b$  are forward and backward rate coefficients ( $\text{T}^{-1}$ ) respectively, which could be obtained by curve fitting, as previously reported.<sup>35,36</sup>. Preliminary fitting procedures allowed us to set forward rate constant  $k_f$  and backward rate constant  $k_b$  to 0.050 and 0.009, respectively.

The three plane model (TPM) was employed to describe the charge of the goethite/water interface, which requires two capacitances for the 0- ( $C_1 = 2.3 \text{ F/m}^2$ ) and the 1-plane ( $C_2 = 1.07 \text{ F/m}^2$ ). Then multi-site complexation (MUSIC) model and PHREEQC-2 was used for modelling the species transport in the GCS-packed column. Though singly ( $\equiv \text{FeOH}^{-0.5}$ ), doubly ( $\equiv \text{Fe}_2\text{OH}$ ) and triply ( $\equiv \text{Fe}_3\text{O}^{-0.5}$  and  $\equiv \text{Fe}_3\text{OH}^{+0.5}$ ) coordinated oxygens exist at the goethite surface, we assumed that NA and NFA trend to bind to reactive  $\equiv \text{FeOH}^{-0.5}$  sites of goethite through HB, OS and even MB (only for NA) complexes based on our studies<sup>18,19</sup>. The reactive site density is given as detailed in our previous work:  $[\equiv \text{FeOH}^{-0.5}] = 3.12 \text{ sites/nm}^2$  and  $[\equiv \text{Fe}_3\text{O}^{-0.5}] = 3.12 \text{ sites/nm}^2$  on (001)/(101) planes (90% of the surface area), and  $[\equiv \text{FeOH}^{-0.5}] = 7.4 \text{ sites/nm}^2$  on (210)/(010) plane (10% of the surface area).

Our modeling strategy is described as follows. Surface hydrolysis and surface complexation reactions including NA/NFA dimer formation were taken from our previous batch sorption study<sup>18</sup>. For the column system, NA and NFA adsorption were first modeled in their respective single systems. The corresponding surface complexation constants were then used to predict binding in the binary system, and the NA-NFA dimer formation constant was calibrated from the experimental data. The column system was described by 1D transport, with  $p$  successive equal width cells ( $\Delta z = L/p$ ,  $L$  is the total column length, in this study  $p = 20$ ). Solution transported between  $p_n$  and  $p_{n+1}$  in time steps  $\Delta t$  and at the defined flow rate and dispersion through the



specific transport procedure implemented into PHREEQC-2. After each time step, this procedure is coupled with the geochemical code for each cell<sup>37</sup>. All parameters used for transport modeling are provided in Table S2.

### 3. Results and discussion

Our previous works<sup>18,19</sup> showed that enhancement in NFA binding, which is otherwise considerably weaker than NA, results from the intermolecular interactions with the goethite-bound NA. We ascribed this enhancement to a NFA-NA dimer whose energetically favored formation (-0.5 eV compared to free molecules) is predominantly driven by van der Waals interactions<sup>19</sup>. For reference, at pH 5, which will be focused in our transport work, NA loadings on goethite (0.33  $\mu\text{mol}/\text{m}^2$ ; 0.20 NA/nm<sup>2</sup>) are more than 3 times larger than NFA ( $\sim 0.10$   $\mu\text{mol}/\text{m}^2$ ; 0.06 NFA/nm<sup>2</sup>) (Fig. S2). Dimer formation in mixed NA and NFA solutions can enhance, in turn, NFA loadings by a factor of  $\sim 2.5$  ( $\sim 0.10 \rightarrow \sim 0.25$   $\mu\text{mol}/\text{m}^2$ ) and NA loadings by  $\sim 1.2$  ( $0.33 \rightarrow \sim 0.40$   $\mu\text{mol}/\text{m}^2$ ) (Fig. S2).

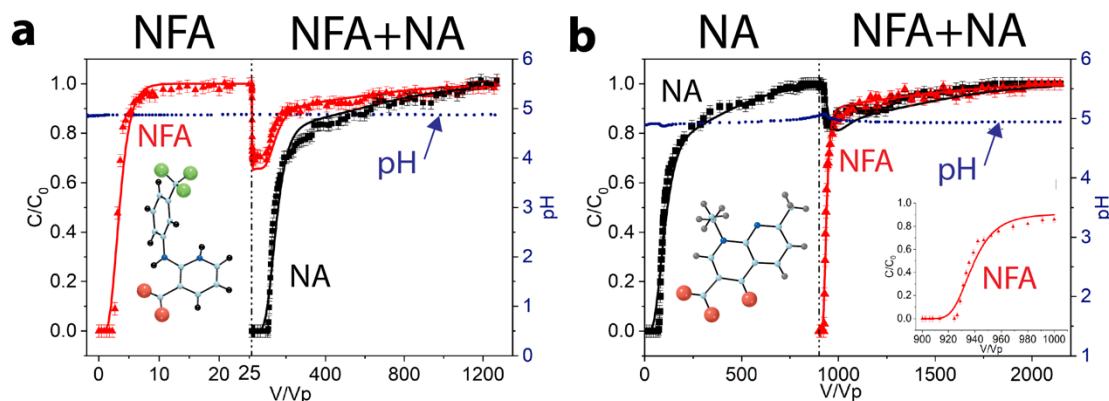
Comparison of this enhancement effect with a suite of other minerals (SI) of contrasting composition and structure shows that NFA binding in the binary system was greatest on goethite. Namely, it followed the order: goethite (2.5-fold) > TiO<sub>2</sub> (2-fold) > magnetite (1.8-fold) > gibbsite (1.5-fold, pH 6)  $\approx$  kaolinite (1.5-fold) > bentonite (1.3-fold)  $\approx$  hematite (1.3-fold). See the SI for a more detailed discussions of these results where we explain that NA-NFA dimer formation is greater on

nanominerals typically with homogeneous distributions of reactive –OH functional groups (goethite, TiO<sub>2</sub>, magnetite), than those typically, with –OH limited to edges of platy minerals with unreactive basal faces (kaolinite, bentonite, hematite). For this reason, we focused our work on the effects of water flow and natural organic matter on NA-NFA interactions using goethite.

### 3.1. NA-NFA dimer formation under water flow

To explore the propensity of NA-NFA dimer formation under flow-through conditions, we performed dynamic flow experiments (Figs. 1, and 2) with columns filled with goethite-coated sand (GCS). First, we find that injection of a mixed solution of NA+NFA after *total breakthrough of NFA* (Fig. 1a) decreased NFA outlet concentrations due to NA-NFA dimer formation on the goethite surface. This started at  $\sim 27$  V/V<sub>p</sub>, reached a plateau at  $\sim 29.5$  V/V<sub>p</sub>, then it gradually increased to a complete breakthrough at  $\sim 1200$  V/V<sub>p</sub>. In contrast, injecting a mixed solution of NA+NFA after *total breakthrough of NA* (Fig. 1b) pushed the breakthrough point of NFA to  $\sim 25$  V/V<sub>p</sub> (insert of Fig. 1b) compared to  $2.3$  V/V<sub>p</sub> in the single system (Fig. S3). The BTC of NFA then tailed extensively before reaching a total breakthrough, thus adopting a classical sigmoidal shape akin to that of NA. Here, NA loadings increased from  $0.68 \mu\text{mol}/\text{m}^2$  in the single system to  $0.90 \mu\text{mol}/\text{m}^2$  in the binary system (Fig. S4), a consequence of the pre-loaded NFA (Fig. 1). Simultaneously injecting NA and NFA after total breakthrough of NA increased both NA and NFA loadings ( $0.90 \mu\text{mol NA}/\text{m}^2$ ;  $0.33 \mu\text{mol NFA}/\text{m}^2$ ), however at levels close to the

values obtained where NFA was first injected (Fig. 1). As a result, we find that NA and NFA exert a mutual effect on their breakthrough behavior under flow and this is basically explained from NA-NFA dimer formation at the goethite surface.



**Figure 1.** The full range of experimental breakthrough curves of NA and NFA through GCS-packed column in two successive steps at constant flow rate (0.5 ml/min). (a) Step I: injection of 10  $\mu$ M NFA and 10 mM NaCl at  $pH_{in} 5 \pm 0.1$  until the complete breakthrough of NFA. Step II: injection of mixture of 10  $\mu$ M NA + 10  $\mu$ M NFA and 10 mM NaCl at  $pH_{in} 5 \pm 0.1$ . The solid lines represent modelling results. (b) Step I: injection of 10  $\mu$ M NA and 10 mM NaCl at  $pH_{in} 5 \pm 0.1$  until the complete breakthrough of NA. Step II: injection of mixture of 10  $\mu$ M NA + 10  $\mu$ M NFA and 10 mM NaCl at  $pH_{in} 5 \pm 0.1$ . Insert is the breakthrough curve of NFA in the initial stage. The solid lines represent modelling results.

Irrespective of the injection scenario, NA exhibits an extended tailing suggesting kinetic limitations under the experimental conditions of this study. Because all of our bromide tracer experiments (Figs. S1 and S5) were well described using the CDE model, the tailing could not be explained by physical non-equilibrium effects, water regionalization into mobile/immobile zones or diffusion limitations between two water zones<sup>38,39</sup>. Moreover, the BTCs of NA and NFA in single systems were compared by normalizing the curves by their retardation factor to that of the bromide

377 tracer (Fig. S6). For NFA, the steepness of BTC showed coincidence with that of  
378 bromide, and only a short tail was observed. However, the normalized BTC of NA  
379 exhibits a significant difference in steepness and shape with respect to that of bromide.  
380 This discrepancy suggests the occurrence of chemical kinetic limitations or  
381 rate-controlled sorption processes under flow-through conditions. This is particularly  
382 the case for transport of the more strongly binding NA. This was confirmed further by  
383 results (Fig. S7) revealing greater NA loadings under conditions of lower flow rate  
384 (0.1 mL/min) that promotes higher residence times.

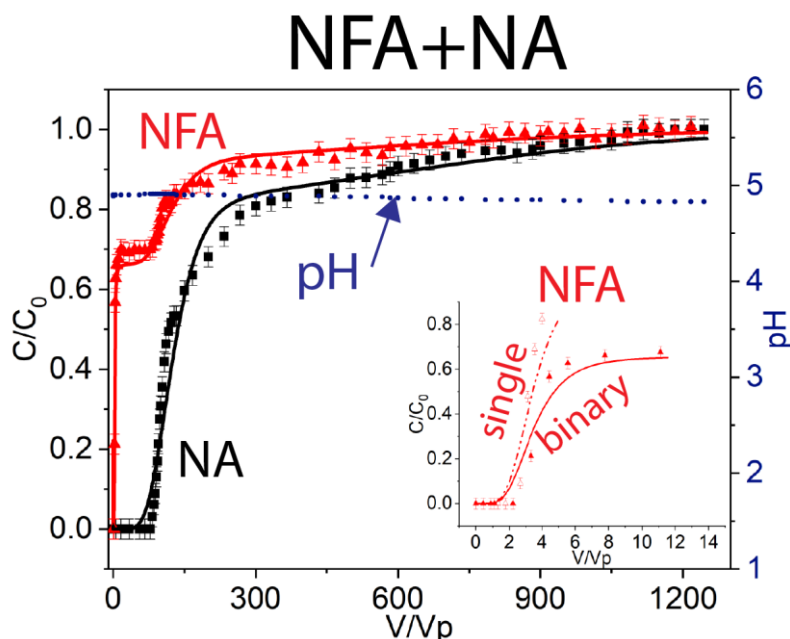
385  
386 To check for the occurrence of kinetic limitations, SCM modeling with or  
387 without kinetics were compared for the BTC of NA (Fig. S8). These results confirmed  
388 that only kinetics implemented with SCM could describe the mobility behavior. In  
389 contrast, the equilibrium SCM seems sufficient for NFA, likely because of weaker and  
390 faster adsorption of NFA mainly through HB and OS complexes<sup>18</sup> (the first stage of  
391 Fig. 1a). However, as NFA adsorption on goethite was strongly related to kinetically  
392 limited NA adsorption, an extended tailing of NFA in the second stage was observed.  
393 As only the sorption kinetics of NA were considered here, we anticipate that this  
394 could affect the adsorption of NFA through co-binding reactions (*cf.* Table S2). Under  
395 such conditions, our combined SCM and kinetics reproduced the mobility of both NA  
396 and NFA (Fig. 1).

397  
398 To provide further evidence for the co-dependency of NA and NFA binding to

GCS, we investigate the transport of the compounds under conditions where both NA and NFA were injected simultaneously (Fig. 2) to a clean column. This revealed two-step breakthrough behavior in the form of two fronts and of two plateaus in the outlet concentration of NFA. This contrasts with the cases of where NFA was injected before (Fig. 1a) or simultaneously with NA (Fig. 2). NFA sorption in the binary system increased sharply to  $0.34 \mu\text{mol}/\text{m}^2$ , compared to that in the single system, yet, they still kept the same breakthrough point at  $2.3 V/V_p$  (insert of Fig. 2). In conclusion, although NA and NFA adopted contrasting BTCs from different injection schemes (NFA/(NFA+NA), NA/(NFA+NA), and (NFA+NA)), their surface loadings after total breakthrough were largely comparable (see Table S3). Here, NA and NFA loadings both increased in the binary compound systems, 1.3 times for NA and 16-19 times for NFA compared to the single system. As such, although NA and NFA transport processes depend on the injection methodology, because of the high-affinity NA to goethite, the injection order has almost no effect on NA and NFA loadings and in the co-binding behavior in the binary systems.

Finally, we confirmed these co-binding effects in experiments conducted at a lower flow rate ( $0.1 \text{ mL}/\text{min}$ ; Fig. S7), where an extended tailing for NA or NFA was also revealed. As a result, the same model previously used in sequential injection has adequately described the behavior of NA and NFA in simultaneous injection approach (Fig. 2).

420



421

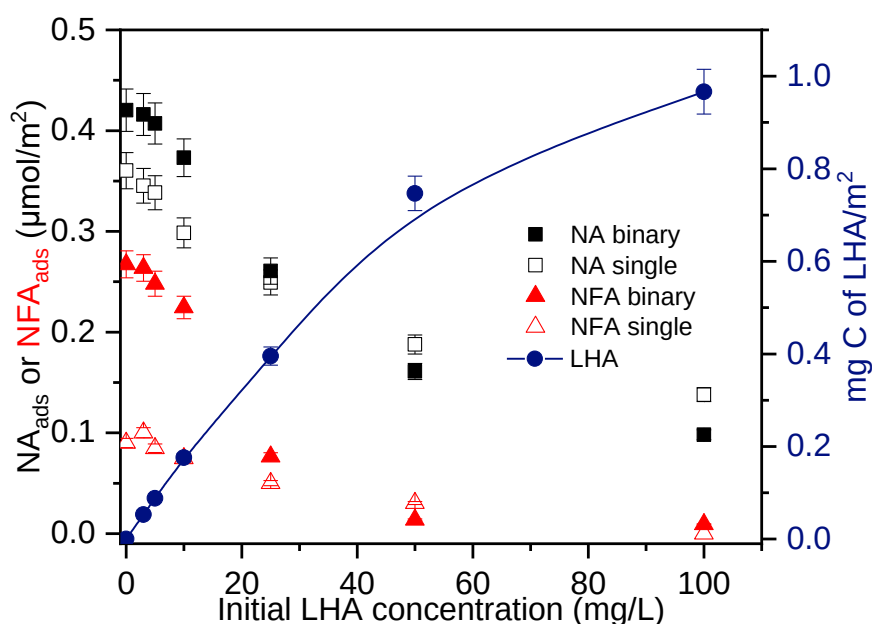
422 **Figure 2.** Experimental and calculated breakthrough curves of NA and NFA in binary  
 423 system at flow rate of 0.5 mL/min through GCS-packed column. Inflowing solution  
 424 contains mixture of 10  $\mu$ M NA and 10  $\mu$ M NFA 10 and 10 mM NaCl at  $pH_{in} = 5 \pm 0.1$ .  
 425 Insert is the breakthrough curves of NFA in the initial stage. The solid lines represent  
 426 modelling results.

427

### 428 3.2 Altered fate of NA and NFA transport by natural organic matter

429 Building upon these results, we evaluated how NOM altered the fate of NA and  
 430 NFA interactions. We used LHA as a representative NOM at loadings of up to  $\sim 1$  mg  
 431  $C/m^2$  ( $\sim 50$  C atoms/ $nm^2$ ) at pH 5 on goethite. From batch adsorption experiments  
 432 (Fig. 3) we find that LHA binding effectively decreased, yet did not completely  
 433 suppress, NA loadings. At the same time, we find that LHA fully suppressed NFA  
 434 co-binding at LHA loadings above  $\sim 0.2$  mg  $C/m^2$  ( $\sim 10$  C/ $nm^2$ ). Based on previous  
 435 work from our group<sup>40</sup>, the goethite surface still exposed unreacted  $-OH$  groups at  
 436 this loading, and is therefore not entirely covered by LHA. Still, bound LHA was

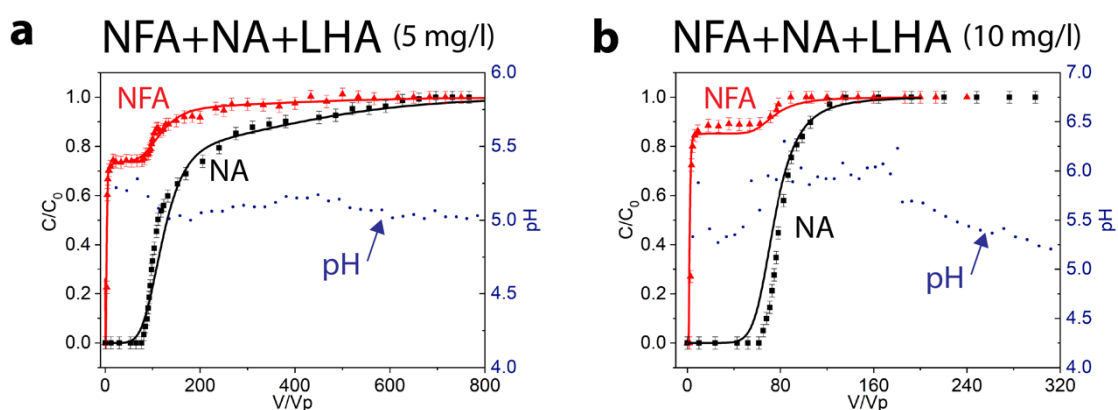
sufficiently effective to prevent binding NFA to the near-interfacial region of goethite for NA/NFA dimer formation. One possible explanation is that LHA altered the interfacial hydration environment and the surface charge of goethite, and thus the potential energy landscape for the NFA diffusion across the goethite/water interface and onto goethite-bound NA. It is also interesting to note that LHA offer no possibilities for NFA binding via, for example, van der Waals  $\pi$ - $\pi$  electron coupling interactions. The enhanced uptake of NFA with NA is therefore driven by a very specific steric control between these two molecules.



**Figure 3.** The effect of humic acid on the adsorption of NA and NFA on 0.5 g/L goethite in single ( $[NA]_{tot} = 20 \mu M$  or  $[NFA]_{tot} = 20 \mu M$ ) and binary ( $[NA]_{tot} = [NFA]_{tot} = 20 \mu M$ ) system at pH 5 and ionic strength 10 mM (NaCl).

Experiments under flow (Fig. 4), again using GCS, showed that LHA at two environmentally-relevant concentrations for groundwater and surface waters<sup>29,30</sup> (5 and 10 mg/L) also affected NA and NFA mobility. Despite the competitive binding

with LHA, co-binding and a two-step breakthrough behavior were still observed (Fig. 4a,b). Small breakthrough times and shorter tailing (steeper BTC) likely resulted from the consumption of adsorption sites by LHA. At relatively low LHA loadings, both NA and LHA compounds bound to goethite surface sites through ligand-exchange and hydrogen bonding, in turn altering the breakthrough behavior of NA. This competitive binding between NA and carboxylic/aromatics compounds of LHA may occur at the first step, followed probably by further adsorption of NA to LHA covered goethite. NFA enhanced adsorption could be clearly observed (from 0.02 to 0.17  $\mu\text{mol}/\text{m}^2$  at 5 mg/L LHA), though this increase was reduced with increasing in LHA amount (from 0.02 to 0.04  $\mu\text{mol}/\text{m}^2$  at 10 mg/L LHA), likely because of the decrease in NA sorption as a result from LHA competitive binding (*cf.* Table S3).



**Figure 4.** Experimental and calculated breakthrough curves of NA and NFA in multicomponent system with LHA at flow rate of 0.5 mL/min through GCS-packed column. a) Inflowing solution contains mixture of 10  $\mu\text{M}$  NA, 10  $\mu\text{M}$  NFA and 5 mg/L of LHA and 10 mM NaCl at  $\text{pH}_{\text{in}} = 5 \pm 0.1$ . b) Inflowing solution contains mixture of 10  $\mu\text{M}$  NA, 10  $\mu\text{M}$  NFA and 10 mg/L of LHA and 10 mM NaCl at  $\text{pH}_{\text{in}} = 5 \pm 0.1$ . The solid lines represent modelling results.



Based on previous studies<sup>20,41,42</sup> we can expect that LHA binding results in a molecular fractionation caused by selective adsorption of heterogeneous LHA components. Lower molecular weight fractions of LHA with higher aromaticity could have primarily, and preferentially, bound to goethite in the first adsorption stage<sup>42</sup>. The higher molecular weight fractions, such as lignin-like and aliphatic compounds, could have, in turn, bound in the following stage<sup>42</sup>. This view falls in line with the breakthrough behavior of LHA in GCS column, particularly in terms of the discrepancy between TOC and UV, which we report in Fig. S9 of the SI. In essence, higher TOC values with respect to UV absorbance at 254 nm were observed during the first adsorption stage. This aligns with the concept that LHA compounds of smaller molecular weight were preferentially adsorbed and successively replaced those of higher weight, as previously reported<sup>37</sup>. The same behavior was previously observed when only LHA was injected in GCS column<sup>20</sup>, suggesting that the presence of NA and NFA did not significantly affect the binding of LHA components in column.

As NOM consists of a polydisperse mixture of organic molecules of varying molecular size, incorporation of complex binding reactions of the LHA components in TLM model is not straightforward. To simplify the model, we only considered sites consumed by LHA components. Then we reduced the available goethite site density (*i.e.* 15 % reduction for 5 mg/L LHA; 60% reduction for 10 mg/L LHA) to describe the modification of NA and NFA BTC in presence of LHA. These results could

suggest that changes in site density were not linearly correlated to LHA loadings, and this could be explained by LHA fractionation and complex interactions with goethite. We have also slightly adjusted the surface NA-NFA dimer formation constant of NA and NFA (Table S2) ( $24.4 \rightarrow 23.8$  for 5 mg/L LHA;  $24.4 \rightarrow 23$  for 10 mg/L LHA) to improve the fit to the data, as the presence of LHA likely alters the formation of NA-NFA dimer. Because of the functional (*e.g.* carboxylates) groups of LHA, the complexation constant of NA on goethite by HB (Table S2) was also modified ( $20.4 \rightarrow 20.6$  for 5 mg/L LHA;  $20.4 \rightarrow 21$  for 10 mg/L LHA). These slight adjustments improved the fit of our model to the experimental data (Fig. 4), and thus our ability to predict multicomponent transport in complex systems. This consequently adds further confidence to the ability of our proposed model to account for NA and NFA (co)-binding under real-world conditions.

## **Environmental implications for environmental fate of pollutant mixtures**

Emerging contaminants such as pharmaceutical compounds in the environment often occur in mixtures rather than as individual entities. The increasing occurrence of multiply contaminated aquatic ecosystems worldwide require efforts to predict synergistic and antagonistic effects affecting the transport of toxic agents in nature.

This study contributes to mounting evidence showing that mobility of pollutant mixtures cannot be predicted based on single-compound based adsorption data. More particularly, we showed that mineral-bound antibiotics can be new adsorption sites for

other contaminants at mineral surfaces. Since this cooperative phenomenon is strongly dependent on the molecular structure of target compound (*e.g.*, possibility of Van der Waals interactions and/or hydrogen bonding), it cannot be generalizable to all pharmaceutical compounds. Indeed, a parallel set of efforts showed that no co-binding occurred with sulfamethoxazole (SMX) neither with NA nor NFA, because of the lack of molecular interactions of SMX with co-existing compounds and goethite surfaces. In contrast, ciprofloxacin (CIP) containing carboxyl and carbonyl functional groups, enhanced NFA binding, because CIP strongly binds to goethite surfaces, and may act as an attachment site for NFA. Therefore, this work raises the importance of recognizing drug co-binding, and lack of co-binding, for accurately predicting the fate of complex pharmaceutical mixtures in the environment.

Flow-through column experiments showed that co-binding caused by intermolecular interactions considerably affects the mobility and transport of NA and NFA in reactive porous media. These new findings combined with batch data and previous theoretical calculations<sup>19</sup> confirmed that the co-binding phenomenon takes place at the mineral surface, and over a wide range of aqueous concentration. Though the concentration in inflow solution may appear higher than the level of aqueous concentration commonly found in aquatic systems<sup>1-5</sup>, continuous flow-through conditions offered the possibility to work with a suitable soil-aqueous phase ratio, and then monitor the effects of dispersion and nonequilibrium sorption on the transport of pollutants. This would certainly bring dynamic-flow tests closer to environmental and real-world conditions.

The presence of environmental level amounts of natural organic matter can reduce the overall retention by minerals, yet it does not suppress cooperative binding. Taking these phenomena into account in a new SCM, which even accounts for kinetic effects, allowed us to predict cooperative adsorption under dynamic flow and non-equilibrium conditions. This new transport model has the potential of successfully predicting the fate of pharmaceutical compounds, as NA and NFA, in various different environmentally relevant scenarios, and over a wide range of concentration including the level amounts commonly detected in environmental systems.

As these co-binding mechanisms at mineral surfaces are not often considered in traditional thermodynamic modeling, our findings raise the importance of recognizing co-binding as a mechanism contributing to the migration of antibiotics and anti-inflammatory agents in complex environmental mixtures. As such, this work contributes to efforts aiming to accurately assess co-binding mechanisms at environmental surfaces, and the fate of co-existing contaminants in the environment.

**Supporting Information.** Synthesis and characterization of minerals; tracer experiments and modeling; co-binding of NA and NFA on different nanominerals; experimental BTCs of NA or NFA with different flow rates and calculated BTCs of NA by using equilibrium and kinetic model in PHREEQC-2. Breakthrough curves of LHA at 5 and 10 mg/L.

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