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## **Co-binding of pharmaceutical compounds at mineral surfaces: mechanistic modeling of binding and co-binding of nalidixic acid and niflumic acid at goethite surfaces**

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27

28 **Abstract**

29 Although emerging contaminants rarely exist individually in environmental  
30 contaminated systems, only limited information on their adsorption mechanisms in  
31 multi-components solutions is currently available. To address this shortcoming, this  
32 work examines for the first time the accuracy of a surface complexation model in  
33 predicting the cooperative adsorption of nalidixic acid (NA) and niflumic acid (NFA) at  
34 goethite ( $\alpha$ -FeOOH) surfaces. Our model adequately predicts co-binding of an  
35 outer-sphere (OS) complex of NFA onto NA bound to goethite through metal bonded  
36 (MB), hydrogen bonded (HB) or OS complexes. More positive charge is introduced in  
37 the system via sodium interactions in order to describe the NFA adsorption at high NaCl  
38 concentrations in both single and binary systems. Our model confidently predicts  
39 multilayers of NA on goethite as well as NFA binding on goethite-bound NA over a  
40 large range of pH, salinity as well as NA and NFA loadings. These findings have strong  
41 implications in the assessment and prediction of contaminant fate in multi-component  
42 contaminated systems by invoking a non-traditional form of ligand-ligand interaction  
43 in this field of study.

## 44 **Introduction**

45        Although emerging contaminants (e.g. pharmaceutical and personal care products)  
46 often exist in mixture in environmental systems<sup>1,2</sup>, they have been often studied  
47 individually with respect to the sorption and/or complexation with naturally occurring  
48 subsurface solids<sup>3,4</sup>. At environmental surfaces, the adsorption of multiple  
49 contaminants (or pollutant mixtures) can give way to competitive or cooperative  
50 binding. While competitive adsorption has been widely investigated<sup>5-7</sup>, very few  
51 studies have resolved the impact of emerging contaminants co-binding at mineral  
52 surfaces. Very recently, we have demonstrated using vibrational spectroscopy and  
53 quantum chemical calculations<sup>8</sup>, that nalidixic acid (NA, a quinolone antibiotic that is  
54 widely used in humans and animals medicine<sup>9</sup>) and niflumic acid (NFA, a non-steroidal  
55 anti-inflammatory that is often used for rheumatoid arthritis<sup>2</sup>) cooperatively adsorb to  
56 naturally-occurring mineral particles by intermolecular interactions (van der Waals).  
57 This novel finding raised the importance of recognizing drug co-binding as a  
58 mechanism contributing to the fate and transport of complex mixtures of antibiotics and  
59 anti-inflammatory agents in nature. Because most traditional environmental models are  
60 based on a single/individual contaminant basis, little is known on their fate in mixed  
61 contaminant systems. Omission of co-binding effects occurring in multi-component  
62 solutions might have unknown consequences on the prediction of fate and transport of  
63 these contaminants in the environment.

64        Some studies have used predictive models involving empirical adsorption isotherm  
65 equations with limited (site specific) applicability to describe the observed data in

66 multi-component solutions<sup>10,11</sup>. However, these macroscopic models cannot account  
67 for co-binding mechanisms for accurately predicting the behavior of antibiotics at  
68 mineral/water interfaces under a large range of physico-chemical conditions. In  
69 contrast, mechanistic models include details of the surface (in terms of structure), take  
70 into account the structure of the electrical interfacial layer<sup>12-14</sup>, and constrain structure  
71 and bonding of surface complexes by information from spectroscopic studies and/or  
72 theoretical calculations<sup>15-17</sup>. Although mechanistic models have extensively been  
73 applied to predict pharmaceutical compounds adsorption to metal-(hydr)oxides<sup>18,19</sup>, no  
74 attempt has been made to account for co-binding mechanisms between two or more  
75 components. This becomes even more important considering the necessity to  
76 adequately account for binding in reactive transport models to be used to predict the  
77 fate of antibiotics and anti-inflammatory agents in nature.

78 In this study, we used molecular-level information (Attenuated Total  
79 Reflectance-Fourier Transform InfraRed (ATR-FTIR) spectroscopy and quantum  
80 chemical calculations) obtained from our previous work<sup>8</sup>, to develop a surface  
81 complexation model to account for the pH and salinity dependence of NA and NFA  
82 loadings achieved at goethite surfaces. We developed, for the first time, a model that  
83 accounts for co-binding of ligands resulting from van der Waals-type interactions. This  
84 opens new possibilities to account these generally overlooked forms of interactions in  
85 these types of studies in the future.

86

## 87 2. Materials and Methods

### 88 2.1. Chemicals

89 All chemicals used were of pro-analytical quality or better and were purchased  
90 from Sigma-Aldrich. Ultrapure water was used in all experiments. Goethite was  
91 prepared following Mazeina and Navrotsky's work<sup>20</sup>. Goethite ( $\alpha$ -FeOOH) was  
92 selected due to its great thermodynamic stability, high surface reactivity with organic  
93 and inorganic ligands, and abundance in soils and sediments<sup>21</sup>. It has been characterized  
94 in detail in our previous work<sup>8</sup>. The specific surface area was of  $81 \pm 4$  m<sup>2</sup>/g and the  
95 isoelectric point (IEP) is 9.1.

96

### 97 2.3. Batch experiments

98 The pH (3-10) and NaCl concentrations (3 – 300 mM) dependences of NA and  
99 NFA binding to goethite was first investigated in single ( $[\text{NA}]_{\text{tot}} = 10$  or  $20$   $\mu\text{M}$  or  
100  $[\text{NFA}]_{\text{tot}} = 20$   $\mu\text{M}$ ) and binary ( $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}} = 20$   $\mu\text{M}$ ) systems. pH adsorption  
101 edges in 10 mM NaCl and adsorption isotherms at pH 6 were taken from previous  
102 work<sup>8</sup>, while pH-dependence of NA and NFA adsorption in single and binary systems at  
103 other NaCl concentrations (3, 100 and 300 mM) were conducted in the present work.  
104 Because high background electrolyte concentrations can affect pH measurements, the  
105 pH electrode was calibrated using solutions of known  $[\text{H}^+]$  ( $10^{-5}$ – $10^{-3}$  M) at different  
106  $[\text{NaCl}]$ . Therefore, pH refers to the molarity of the proton ( $-\log [\text{H}^+]$ ). Adsorption  
107 isotherms were obtained by experiments with (i) equimolar concentrations of NA and  
108 NFA (0.1 - 100  $\mu\text{M}$ ), (ii) varying concentrations of NFA (0.1 - 100  $\mu\text{M}$ ) with 20  $\mu\text{M}$

109 NA, and (iii) varying concentrations of NA (0.1 - 100  $\mu\text{M}$ ) with 20  $\mu\text{M}$  NFA.  
110 Additionally, desorption tests conducted at  $\text{pH} = 11$  were used to verify the mass  
111 balance of NA and NFA in the suspensions. They showed that solutes were removed  
112 only by adsorption, and that transformations by, for example, oxidation, did not occur  
113 under our experimental conditions (a result that is consistent with previous  
114 findings<sup>22</sup>).

115 Batch experiments were conducted in 10 mL suspensions of 0.5 g/L goethite in  
116 polypropylene tubes under an atmosphere of  $\text{N}_2(\text{g})$  in order to avoid the effect of  
117 dissolved  $\text{CO}_2$ . Suspensions were mixed for a period of 8 h by end-over-end shaking,  
118 which is sufficient to reach a steady state<sup>8</sup>. Aliquots of the resulting suspensions were  
119 thereafter sampled and filtered (0.2  $\mu\text{m}$ ) for analysis. All adsorption experiments were  
120 performed at least twice, with a reproducibility of  $\sim 5\%$  for NA- and  $\sim 10\%$  for  
121 NFA-bearing systems.

122 Aqueous concentrations of NA and NFA were determined using high performance  
123 liquid chromatography (Waters 600 Controller) equipped with a photodiode array  
124 detector (Waters 996) and a reversed-phase C18 column (250 mm $\times$ 4.6 mm i.d., 5  $\mu\text{m}$ ).  
125 The mobile phase (1 mL/min) was a mixture of acetonitrile/water (60/40 v/v) contained  
126 0.1% formic acid. The detector was set to 258 nm for NA, 283 nm for NFA and both  
127 molecules could be analyzed with a single injection (NA: 4.5 min; NFA: 10.1 min).

128

#### 129 **2.4. Surface complexation modeling**

130 The geochemical speciation code PHREEQC (version 2)<sup>23</sup> was used for surface

131 complexation calculations using thermodynamic database of Minteq. The  $pK_a$ s of NA  
132 ( $pK_a=6.19$ ) and NFA ( $pK_{a,1}=2.28$  and  $pK_{a,2}=5.10$ ) at infinite dilution were obtained  
133 from conditional  $pK_a$  values<sup>24,25</sup> and the Davies equation. NA exists as neutral (NAH,  
134  $pH < pK_a$ ) or anionic form ( $NA^-$ ,  $pH > pK_a$ ), and NFA as cationic ( $NFAH_2^+$ ,  $pH < pK_{a,1}$ ),  
135 anionic ( $NFA^-$ ,  $pH > pK_{a,2}$ ), neutral ( $NFAH^0$ ) or zwitterionic form ( $NFAH^{+/-}$ ) at  $pK_{a,1} <$   
136  $pH < pK_{a,2}$ . Molecular structures of the different dissolved NA and NFA species and  
137 calculated NA and NFA speciation versus pH in 10 mM NaCl solution are shown in  
138 Figure S1. Protonation reactions of NA and NFA are given in Table 1.

139 The charge of the goethite/water interface was treated with using the three plane  
140 model (TPM)<sup>13</sup>, where charges of the adsorbates can be distributed between the 0-  
141 (metal-bonded complexes), 1- (hydrogen-bonded complexes), and 2-planes ( $Na^+$ ,  $Cl^-$ ,  
142 outer-sphere complexes). The TPM requires two capacitances for the 0- ( $C_1$ ) and the  
143 1-plane ( $C_2$ ) which were taken from a previous study in our group<sup>26</sup>. Predictions of NA  
144 and NFA adsorption to goethite were made using the multi-site complexation (MUSIC)  
145 model<sup>12</sup>. For goethite, different types of surface sites can exist depending of the  
146 proportion of crystal planes, which should have different binding affinities. The  
147 goethite surface is considered to exhibit (101), (001) and (210) planes (group Pnma),  
148 which represent 63%, 27% and 10% of the total surface area, respectively. Singly  
149 ( $\equiv FeOH^{-0.5}$ ), doubly ( $\equiv Fe_2OH$ ) and triply ( $\equiv Fe_3O^{-0.5}$  and  $\equiv Fe_3OH^{+0.5}$ ) coordinated  
150 oxygens can be found at the goethite surface, depending on the crystal face. To simplify  
151 the model, we adopted the 1-pK approximation of the MUSIC model<sup>12</sup>, neglecting the  
152 contributions of doubly- and part of the triply-coordinated oxygens. Crystallographic

153 site densities in this model are:  $[\equiv\text{FeOH}^{-0.5}] = 3.03$  sites/nm<sup>2</sup> at the (101), 3.34 sites/nm<sup>2</sup>  
154 at the (001) and 7.4 sites/nm<sup>2</sup> at the (210) planes, and  $[\equiv\text{Fe}_3\text{O}^{-0.5}] = 3.03$  sites/nm<sup>2</sup> at the  
155 (101) and 3.34 site/nm<sup>2</sup> at the (001) planes. The protonation constants of the groups are  
156 set to that of the IEP (1-pK approach<sup>14</sup>). Formation constants of all surface species are  
157 reported in Table 1.

158 NA and NFA are considered to bind only to  $\equiv\text{FeOH}^{-0.5}$  groups. From a molecular  
159 viewpoint, ligands might also form H-bonds with doubly ( $\equiv\text{Fe}_2\text{OH}$ ) and triply  
160 ( $\equiv\text{Fe}_3\text{O}^{-0.5}$  and  $\equiv\text{Fe}_3\text{OH}^{+0.5}$ ) coordinated sites. Recently, Boily<sup>27</sup> showed that  
161 protonation of doubly-coordinated hydroxo groups and one type of triply-coordinated  
162 oxo group, which are considered to be proton-silent within the 1-pK approach, may be  
163 favored in the presence of strongly binding negatively charged ligand. However, a full  
164 version of the MUSIC model for goethite would be required to account for all these  
165 sites. This would lead to a drastic increase in the number of parameters and then  
166 complexity in the model, and thus not considered in this modeling approach, as  
167 generally carried out in literature<sup>17-19,26,28-30</sup>.

168 The modeling strategy proceeded as follows. First, NA and NFA adsorption was  
169 modeled in single systems. The corresponding surface complexation constants were  
170 kept constant to model the NA-NFA binary system. All surface complexes reactions  
171 involved in binding and co-binding mechanisms were proposed based on our own  
172 molecular-level information and theoretical calculations and literature data, as detailed  
173 below in section 3.

174 PhreePlot<sup>31</sup> was used to determine surface complexation constants and related

175 uncertainties for NA and NFA adsorption to goethite (single and binary systems).  
176 Charge variations at the 0-, 1- and 2-planes ( $\Delta z_0$ ,  $\Delta z_1$ ,  $\Delta z_2$ , respectively) are constrained  
177 by spatial considerations and are not adjustable parameters. PhreePlot contains an  
178 embedded version of the geochemical speciation program PHREEQC and it includes a  
179 parameter optimization procedure, which automatically fits a model to experimental  
180 data by minimizing the weighted sum of squares of the residuals. A modified  
181 Marquardt–Levenberg procedure was applied<sup>32</sup>. With this method, PhreePlot provides  
182 also a statistical uncertainty of the estimated parameters, which is given for each of  
183 optimized parameters in Table 1. Note that PHREEQC version 2 uses surface coverage  
184 fractions as standard state for surface species<sup>33,34</sup>.

185

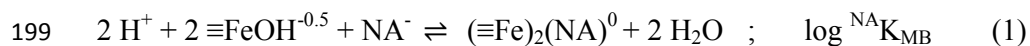
### 186 **3. Results and discussion**

187 **3.1. Nalidixic acid (NA) adsorption on goethite (single system).** As typically  
188 observed for many organic ligands, NA adsorption versus pH showed a bell-shape, and  
189 the maximum adsorption amount was observed at a pH near the  $pK_a$  (Fig. 1a).  
190 Increasing NaCl concentration decreased NA adsorption on the whole investigated pH  
191 range ( $[NA]_{tot} = 20 \mu M$ ; Fig. 1), an effect that is generally attributed to non-specifically  
192 bound ligands at mineral surfaces<sup>29,35</sup>.

193 According to the spectroscopic investigations of NA binding to goethite<sup>8</sup> and in  
194 agreement with previous studies on quinolone binding to minerals<sup>29,36</sup>, MB surface  
195 complexes at the goethite (101)/(001) and (210) planes (Pnma group) were expected to

196 form *via* a NA keto group and one oxygen of the carboxylate group. This can be  
197 expressed through the surface complexation reaction:

198

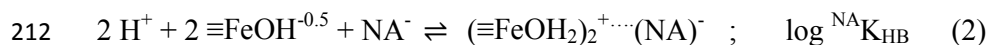


200

201 Only singly coordinated ( $\equiv\text{FeOH}^{-0.5}$ ) surface sites were considered to be involved in the  
202 latter reaction given the propensity for ligand exchange of these sites. Eq. 1 does not  
203 denote the number of Fe(III) octahedra in a complex, but only the number of  $\equiv\text{FeOH}^{-0.5}$   
204 sites that may or may not be of the same Fe(III) octahedron<sup>30</sup>. Ideally, the steric  
205 constraints at the dominant (101)/(001) planes (Pnma group) should promote bridging  
206 between two Fe atoms separated by 3 Å from one another<sup>37</sup>, while at the (210) plane,  
207 two  $\equiv\text{FeOH}^{-0.5}$  should be located on the same Fe(III) octahedron, hence our preference  
208 for modeling NA binding as a 1:2 NA: $\equiv\text{FeOH}^{-0.5}$  species (Table 1).

209 Hydrogen-bonded (HB) complexation (surface hydration-shared ion pair) was  
210 also modeled through singly  $\equiv\text{FeOH}^{-0.5}$  sites with:<sup>30</sup>

211



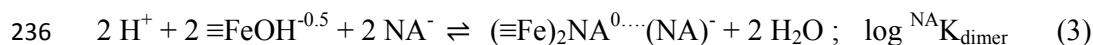
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214 Formation of an outer-sphere (OS) complex (solvent-surface hydration-separated ion  
215 pair), where NA keeps its first hydration sphere and its charge is located in the 2-plane,  
216 was also considered to form with protonated singly-coordinated sites ( $\equiv\text{FeOH}_2^{+0.5}$ )  
217 (Table 1).

218 As shown in Figure S2, our model satisfactorily predicts the pH dependence of NA  
 219 adsorption to goethite at low NA loading ( $[NA]_{tot} \leq 20 \mu\text{M}$ ; Fig. S2a,b,c), but  
 220 underestimated the NA adsorption isotherm at pH 6 at high NA loadings (Fig. S2d).  
 221 Furthermore, the effect of NaCl concentration on NA adsorption is not very well  
 222 captured in this model, since this effect is small for  $[NA]_{tot} = 10 \mu\text{M}$  (Fig. S2a) but large  
 223 for  $[NA]_{tot} = 20 \mu\text{M}$  (Fig. S2a,b). The corresponding highest adsorbed amount lies at  
 224  $0.85 \text{ NA}/\text{nm}^2$  (i.e.  $1.4 \mu\text{mol}/\text{m}^2$ ), and did not exceed the estimated NA loadings of  $\sim 1.5$   
 225  $\text{NA}/\text{nm}^2$  that can be expected if all the  $\sim 3 \text{ -OH}/\text{nm}^2$  were to be consumed. Attempts to  
 226 reproduce our data with the model of Boily<sup>27</sup> (i.e. using a full version of the MUSIC  
 227 model for goethite including more surface sites for HB and OS complexes) led to  
 228 similar conclusions (not shown). We thus conclude that calculated NA adsorption  
 229 amount at high loading is not limited by the number of available surface sites, but by  
 230 less favorable electrostatic effects due to surface charge neutralization by NA.

231 In fact, higher loadings favor additional binding mechanisms (e.g. multilayer,  
 232 dimerization, hydrophobic interactions and surface precipitation) involving direct  
 233 NA-NA interactions. Drawing from our previous work on intermolecular interactions  
 234 between naphthoic acids<sup>16</sup>, we can write:

235



237

238 In this equation, a NA-NA dimer is formed by co-bonding to individual NA molecules,  
 239 resulting in an interfacial distribution of charges between the 0- and 1-planes.

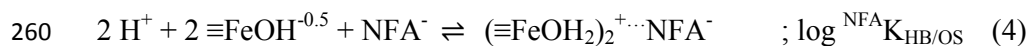
240 Combining the equations with monomer and dimer of NA, the model better predicts  
241 NA adsorption at high loadings (Fig. 1d).

242 In summary, surface complexation modeling results (Table 1, Fig. 1 and Fig. S3),  
243 predict NA binding as a function of pH (Fig. 1a and Fig. S3 for  $[NA]_{tot} = 20$  and  $10 \mu\text{M}$ ,  
244 respectively), NaCl concentration (Fig. 1 a,c) and NA loadings (Fig. 1d). In accordance  
245 with previous reports on ligand binding (e.g. for benzenecarboxylates<sup>30</sup>), NA  
246 predominantly formed HB and OS complexes at high pH while MB complexes only  
247 formed at  $\text{pH} < 7$  (Fig. 1a). The model also predicts NA dimer formation with NA  
248 between pH 3 and 7 (Fig. 1 a,d).

249

250 **3.2. Niflumic acid (NFA) adsorption on goethite (single system).** NFA binding  
251 followed the same pH dependence as NA (Fig. 1b) but is favored at NaCl concentration  
252 greater than 50 mM (Fig. 1c). This alongside the weaker dependence of binding on  
253 NFA loadings (Fig. 1d) suggests distinct binding mechanisms to those of NA. In fact,  
254 based on the disposition of its functional groups, HB and OS complexation should  
255 predominate over MB species under all conditions considered in this work, as for  
256 example for other monocarboxylate ligands such as acetate, benzoate,  
257 cyclohexanecarboxylate or naphthoate<sup>17,35</sup>. Both HB and OS complexes were  
258 expressed by the following reaction:

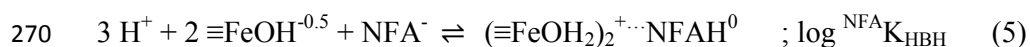
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261

262 here omitting the intervening roles of water. The -1 charge of the HB complex of NFA  
 263 is located at the 1-plane ( $\Delta z_1 = -1$ ;  $\Delta z_2 = 0$ ) whereas that of the OS complex is in the  
 264 2-plane ( $\Delta z_1 = 0$ ;  $\Delta z_2 = -1$ ). This model adequately accounts for all goethite-NFA data,  
 265 except the effect of NaCl concentration. Alternatively, replacing the HB complex with  
 266 its zwitterion form provides both an adequate prediction of binding with pH and NaCl  
 267 concentration below pH 6, and is consistent with previous accounts<sup>18,19,38</sup> supporting  
 268 this type of species.

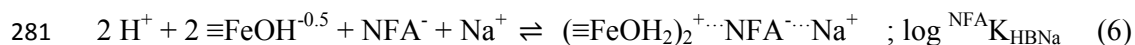
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271

272 Preliminary calculations showed that HB complexes with anionic or zwitterionic form  
 273 of NFA occurred in a comparable pH-range (not shown). To simplify the model, the  
 274 HB complex with the anionic form was removed from the speciation scheme. The OS  
 275 species is however needed to account for the high pH data at NaCl concentrations  
 276 below 10 mM. This model accurately predicts NFA adsorption at 10 mM NaCl but  
 277 provides a poor description of NaCl effect (Fig. S4). Because of the increasing  
 278 adsorption of NFA at high NaCl concentration, a sodium-OS ion pair is however  
 279 needed to account for the data above 10 mM NaCl through:

280



282

283 where  $\text{Na}^+$  charge is located in the 2-plane. Sodium co-binding has been previously  
284 proposed to describe the adsorption of phosphate to goethite<sup>39</sup>. This model allows a  
285 relatively good prediction of NFA adsorption to goethite at various pH (Fig. 1b),  
286 [NaCl] (Fig. 1b,c) and [NFA] (Fig. 1d).

287

### 288 **3.3. Binary NA-NFA system**

289 NA-NFA co-binding occurred over a large range of pH (Fig. 2a,b), NaCl  
290 concentrations (Fig. 2a,b,e) and NA and NFA loadings (Fig. 2c,d). Co-binding effect is  
291 more pronounced for NFA, because of its weaker adsorption in single system.  
292 However, NA adsorption to goethite is rather strong in single system, and so co-binding  
293 with NFA only further stabilizes NA at the surface. As a result, to accurately predict  
294 binding in mixed NA-NFA system, the model requires reactions accounting of  
295 cooperative effects between NA and NFA besides the competitive binding mechanisms  
296 of eqs. 1-6. This is further illustrated in Figure S5, where NA and NFA adsorption in  
297 binary system is strongly underestimated when using only eqs. 1-6.

298 For NA, all MB, HB and OS complexes of NA are considered to be formed  
299 because of the similar shape of the adsorption edges in mixtures with those of the single  
300 system (Figs. 1a and 2a), while only OS complexes are considered for NFA because the  
301 maximal loadings of NFA (Fig. 2b) coincided with that achieved in the single system  
302 (Fig. 1b). To keep the model at a reasonable level of complexity we however only  
303 considered the binary NA-NFA surface complex at the (101)/(001) planes and model  
304 co-binding with:

305



308



311



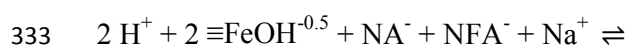
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315 In eq. 7-9, NFA binds to one NA at the goethite surface predominantly via van der  
 316 Waals interactions<sup>8</sup>, and its -1 charge is located at the 2-plane. In contrast, NA is  
 317 assumed to form MB, HB and OS complexes with goethite, respectively, and its -1  
 318 charge should therefore be located at the 0-plane ( $\Delta z_0=+1$ ;  $\Delta z_1=0$ ;  $\Delta z_2=-1$ , eq. 7), the  
 319 1-plane ( $\Delta z_0=+2$ ;  $\Delta z_1=-1$ ;  $\Delta z_2=-1$ , eq. 8) or the 2-plane ( $\Delta z_0=+2$ ;  $\Delta z_1=0$ ;  $\Delta z_2=-2$ , eq. 9).  
 320 Note that the reverse case (NA binding to adsorbed NFA) involves the same  
 321 stoichiometry and charge distribution over the 0-, 1- and 2-planes. Therefore, they are  
 322 equivalent in PHREEQC. However, previous quantum chemical calculations<sup>8</sup>  
 323 suggested that the reverse case was less plausible, that is, NA was expected to be  
 324 located closer than NFA to the surface.

325 Our first modeling attempts using eqns. 1-9 predicted a decrease of NA/NFA  
 326 adsorption with increasing [NaCl], which is inconsistent with experimental

327 observations (see Figure S6). Most notably, experimental NA binding became almost  
 328 independent of NaCl concentration (Fig. 2a,e) while NFA binding followed three  
 329 stages: (i) slight decrease in loadings below 10 mM, (ii) increased loadings at 10-50  
 330 mM, and (iii) constant loadings above 50 mM NaCl (Fig. 2b,e). Including of an ion pair  
 331 with sodium

332



335

336 considerably improved model predictions of the effect of NaCl (Fig. 2a,b,e). The best  
 337 fit was obtained by allocating charges of both NA and NFA in the 1-plane and  $\text{Na}^+$  in  
 338 the 2-plane ( $\Delta z_0=+2$ ;  $\Delta z_1=-2$ ;  $\Delta z_2=+1$ ) (Table 1).

339 The full model (i.e. eqs.1-10) provides an accurate description of co-binding data  
 340 vs pH and NaCl concentration (Fig. 2a, b) and at a wide range of aqueous concentration  
 341 (0.1- 100  $\mu\text{M}$ ) (Fig. 2c). This also permits to fit very well the variation of  $[\text{NFA}]_{\text{ads}}$  as a  
 342 function of  $[\text{NA}]_{\text{ads}}$  regardless of the adopted approach : (i) varying  $[\text{NA}]_{\text{tot}}$  at constant  
 343  $[\text{NFA}]_{\text{tot}}$ , (ii) varying  $[\text{NFA}]_{\text{tot}}$  at constant  $[\text{NA}]_{\text{tot}}$  or (iii) varying equimolar  
 344 concentration of both (Fig. 2d).

345 Model predictions of NA and NFA surface speciation for 10 mM NaCl (Figs. 2 a,b)  
 346 suggest that NA-NFA dimers remarkably prevail at  $\text{pH} > 4$ . Although NA adsorption  
 347 slightly increased from the single to the binary system, its surface speciation drastically  
 348 changes, probably due to competition between the three forms of NA (NA monomer,

349 NA dimer and NA-NFA dimer). Indeed, proportions of monomeric and dimeric forms  
350 of NA strongly diminished in favor of NA-NFA surface complexes (Fig. 2a, c). NFA  
351 adsorption was, however, mainly dominated by the formation of NA-NFA surface  
352 complexes (Fig. 2b, c).

353 Finally, our proposed model not only explains batch adsorption data generated for  
354 this work but also concentration profiles of dominant species extracted by a  
355 chemometric analysis<sup>40</sup> of our previously published<sup>8</sup> Fourier Transform Infrared  
356 spectra on these systems (Fig. 2f). Our work had shown that vibration spectra of mixed  
357 NA+NFA+goethite could not be explained as a linear combination of isolated  
358 NA+goethite and NFA+goethite systems. The concentration profiles in Fig. 2f show  
359 that increasing fractions of NA-NFA complexed with increasing  $[NA]_{tot}$  (constant  
360  $[NFA]_{tot}$ ) or with increasing  $[NFA]_{tot}$  ( $[NA]_{tot}$ ) are well-predicted by the model. This  
361 adds further confidence to the ability of our proposed model to account for NA and  
362 NFA binding in single and mixed systems.

363

364 **Implications for reactive transport modeling.** Because of the increase of multiple  
365 contaminations in aquatic ecosystems worldwide, environmental subsurface and  
366 groundwaters often contain multiple contaminants including nonprescription drugs,  
367 antibiotics, hormones and prescription drugs<sup>41</sup>. Protection of groundwater resources  
368 requires an accurate assessment of processes controlling the contaminant fate and  
369 transport in complex environmental mixtures.

370 The development of new surface complexation models to account for co-binding at

371 mineral surfaces is central to the prediction of the fate of contaminants in  
372 multi-component systems. We demonstrate, for the first time, that co-binding of  
373 emerging organic contaminants (e.g. NA and NFA) can be predicted over a large range  
374 of environmentally relevant conditions using a mechanistic model based on insights  
375 from vibration spectroscopy and quantum chemical calculations<sup>8</sup>. The modeling  
376 approach accounting for new forms of drugs co-binding at mineral surfaces is  
377 becoming a powerful tool for implementation of co-binding phenomena in reactive  
378 transport models, and for the accurate prediction of the transport of antibiotics and  
379 anti-inflammatory agents in soils and sediments.

380

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386

### 387 **Supporting information available**

388 NA and NFA aqueous speciation versus pH and additional modeling tests. This  
389 information is available free of charge via the Internet at <http://pubs.acs.org/>.

390

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392

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- 510
- 511

512 **Table 1. Model parameters.**

	Complex	log K	$\Delta z_0$	$\Delta z_1$	$\Delta z_2$
$\text{NA}^- + \text{H}^+ = \text{NAH}$		6.19			
$\text{NFA}^- + \text{H}^+ = \text{NFAH}$		5.10			
$\text{NFAH} + \text{H}^+ = \text{NFAH}_2^+$		2.28			
$\equiv\text{Fe}_3\text{O}^{-0.5} + \text{H}^+ \rightleftharpoons \equiv\text{Fe}_3\text{OH}^{+0.5}$		9.1	+1	0	0
$\equiv\text{Fe}_3\text{O}^{-0.5} + \text{H}^+ + \text{Cl}^- \rightleftharpoons \equiv\text{Fe}_3\text{OH}_2^{+0.5}\cdots\text{Cl}^-$		8.1	+1	0	-1
$\equiv\text{Fe}_3\text{O}^{-0.5} + \text{Na}^+ \rightleftharpoons \equiv\text{Fe}_3\text{OH}^{-0.5}\cdots\text{Na}^+$		-1	0	0	+1
$\equiv\text{FeOH}^{-0.5} + \text{H}^+ \rightleftharpoons \equiv\text{FeOH}_2^{+0.5}$		9.1	+1	0	0
$\equiv\text{FeOH}^{-0.5} + \text{H}^+ + \text{Cl}^- \rightleftharpoons \equiv\text{FeOH}_2^{+0.5}\cdots\text{Cl}^-$		8.1	+1	0	-1
$\equiv\text{FeOH}^{-0.5} + \text{Na}^+ \rightleftharpoons \equiv\text{FeOH}^{-0.5}\cdots\text{Na}^+$		-1	0	0	+1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- \rightleftharpoons (\equiv\text{Fe})_2(\text{NA})^0 + 2 \text{H}_2\text{O}$	MB	19.7±0.1	+1	0	0
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-$	HB	20.0±0.1	+2	-1	0
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-$	OS	20.8±0.1	+2	0	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + 2 \text{NA}^- \rightleftharpoons (\equiv\text{Fe})_2(\text{NA})^0 \cdots \text{NA}^-$	dimer	22.2±0.1	+1	-1	0
$3 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NFAH}$	HBH	27.0±0.1	+2	0	0
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NFA}^-$	OS	19.9±0.1	+2	0	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NFA}^- + \text{Na}^+ \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NFA}^-\cdots\text{Na}^+$	HB-Na	20.8±0.1	+2	-1	+1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- \rightleftharpoons (\equiv\text{Fe})_2(\text{NA})^0 \cdots \text{NFA}^-$	MB-OS	23.2±0.2	+1	0	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-\cdots\text{NFA}^-$	HB-OS	23.2±0.2	+2	-1	-1
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-\cdots\text{NFA}^-$	OS-OS	25.4±0.2	+2	0	-2
$2 \text{H}^+ + 2 \equiv\text{FeOH}^{-0.5} + \text{NA}^- + \text{NFA}^- + \text{Na}^+ \rightleftharpoons (\equiv\text{FeOH}_2)_2^+\cdots\text{NA}^-\text{NFA}^-\cdots\text{Na}^+$	HB-HB-Na	26.3±0.2	+2	-2	+1

513

514 TPM with  $C_1=2.3 \text{ F/m}^2$ ,  $C_2=1.07 \text{ F/m}^2$ ; 63% of (101), 27% of (001) and 10% of (210). Site  
515 densities:  $[\equiv\text{FeOH}^{-0.5}]=3.03$ , 3.34 and 7.4 site/nm<sup>2</sup> at the (101), (001) and (210) planes,  
516 respectively;  $[\equiv\text{Fe}_3\text{O}^{-0.5}]=3.03$  and 3.34 site/nm<sup>2</sup> at the (101) and (001) planes, respectively. HB,  
517 OS and binary NA-NFA complexes are considered to form at all planes ((101)/(001)/(210)). NA  
518 and NFA surface complexation constants and uncertainty obtained with Phreeplot. All other  
519 parameters were fixed.

520

521 **Figure captions**

522

523 **Figure 1.** Single systems. Adsorption of 20  $\mu\text{M}$  (a) NA and (b) NFA to goethite (0.5  
524 g/L) versus pH and  $[\text{NaCl}]$  (3-100 mM). (c) Adsorption of 20  $\mu\text{M}$  NA or NFA (20  $\mu\text{M}$ )  
525 on goethite (0.5 g/L) versus  $[\text{NaCl}]$  at pH 5. (d) NA-goethite and NFA-goethite  
526 adsorption isotherms at pH 6 in 10 mM NaCl, where NA surface speciation is shown  
527 (“total” refers to overall modeled adsorption results). In all graphs, full lines correspond  
528 to overall adsorption predicted by surface complexation modeling. In (a) and (b) NA  
529 and NFA surface speciation is shown as discontinuous lines (for 10 mM NaCl). MB,  
530 HB and OS denote metal-bonded, hydrogen-bonded and outer-sphere complexes,  
531 respectively.

532

533 **Figure 2.** Binary NA-NFA system. Adsorption of (a) NA and (b) NFA to goethite (0.5  
534 g/L) versus pH and  $[\text{NaCl}]$  (3-300 mM) for  $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}} = 20 \mu\text{M}$ . (c) NA and  
535 NFA adsorption isotherms at pH 6 in 10 mM NaCl for  $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}}$ . (d)  $[\text{NFA}]_{\text{ads}}$   
536 vs  $[\text{NA}]_{\text{ads}}$  for three experimental conditions: (i) ( $[\text{NFA}]_{\text{tot}} = 20 \mu\text{M}$ , varying  $[\text{NA}]_{\text{tot}}$ ,  
537 black), (ii) ( $[\text{NA}]_{\text{tot}} = 20 \mu\text{M}$ , varying  $[\text{NFA}]_{\text{tot}}$ , red), and (iii) varying both compounds  
538 with  $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}}$  (blue). (e) Adsorption of NA and NFA ( $[\text{NA}]_{\text{tot}} = [\text{NFA}]_{\text{tot}} = 20$   
539  $\mu\text{M}$ ) on goethite (0.5 g/L) versus  $[\text{NaCl}]$  at pH 5. In all graphs, full lines correspond to  
540 overall adsorption predicted by surface complexation modeling (using the same color  
541 as the corresponding symbol). In (a), (b) and (c) NA and NFA surface speciation is  
542 shown as discontinuous lines (for 10 mM NaCl). “total” refers to overall modeled  
543 adsorption results in (c). (f) Concentration profiles extracted by chemometric modeling  
544 of FTIR data<sup>8</sup> for the series corresponding to constant  $[\text{NA}]_{\text{tot}}$  and varying  $[\text{NFA}]_{\text{tot}}$   
545 (black) or constant  $[\text{NFA}]_{\text{tot}}$  and varying  $[\text{NA}]_{\text{tot}}$  (red).

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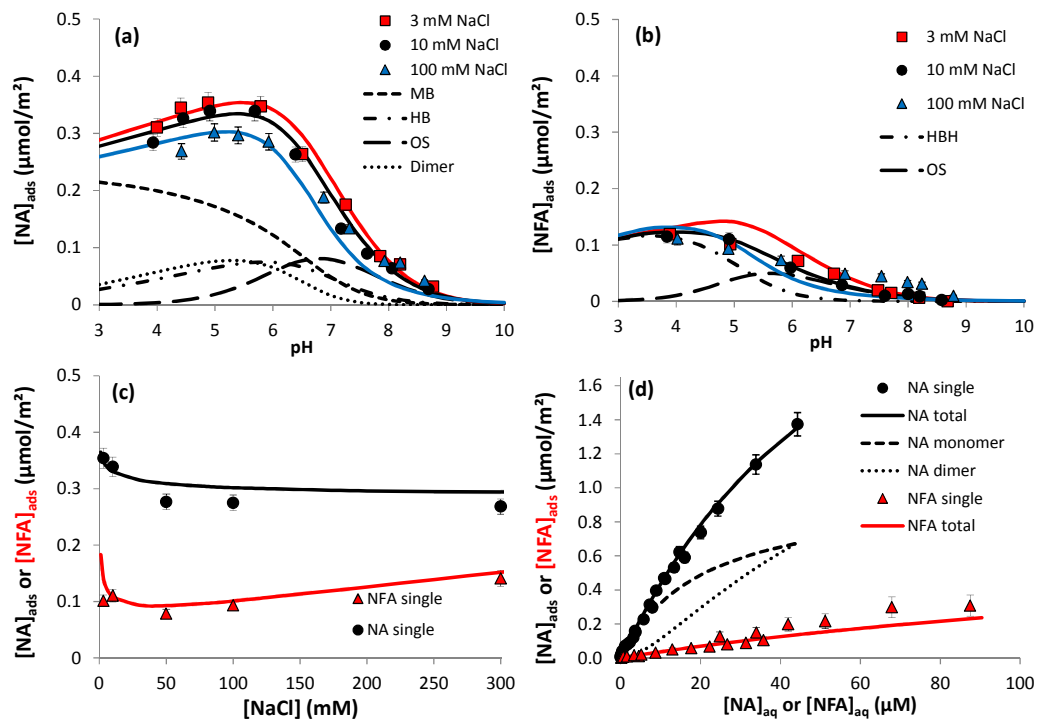
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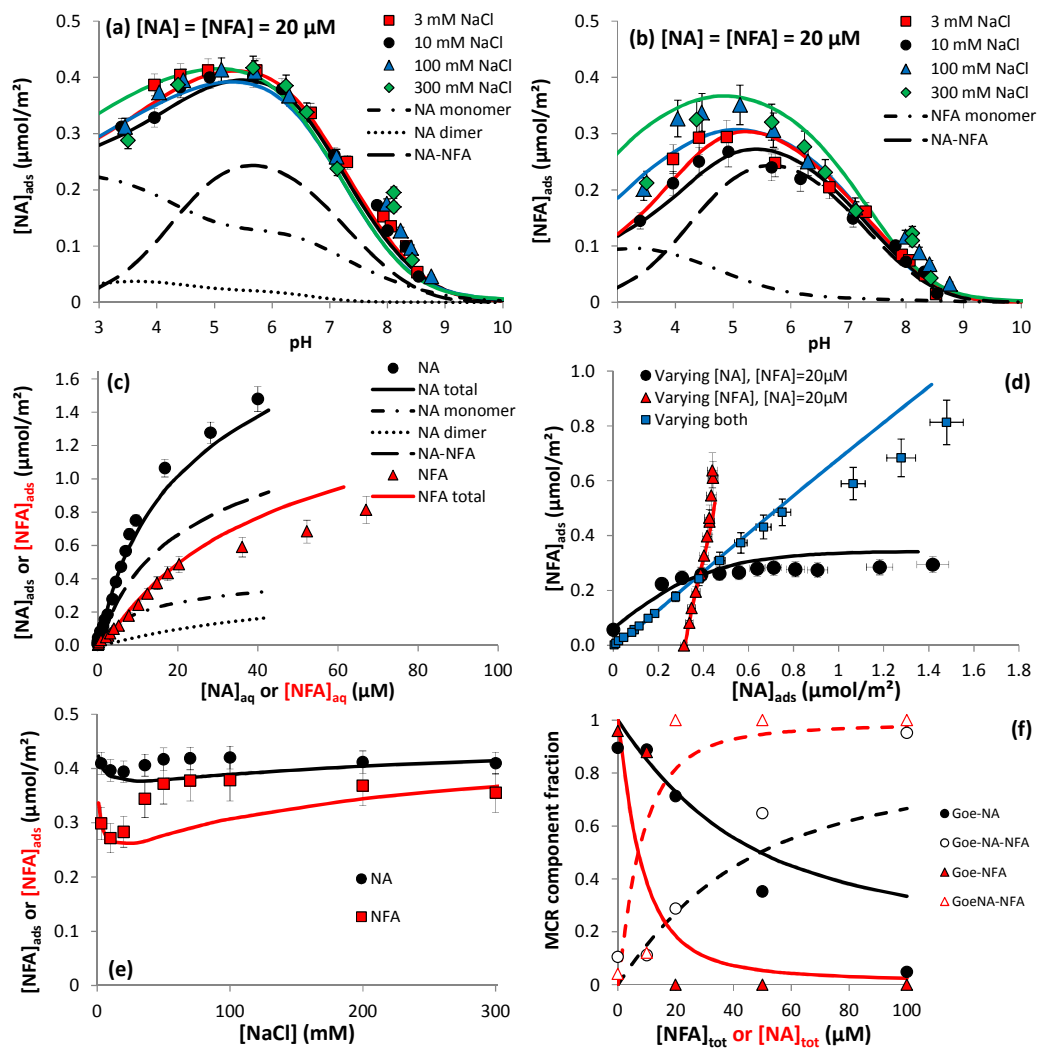
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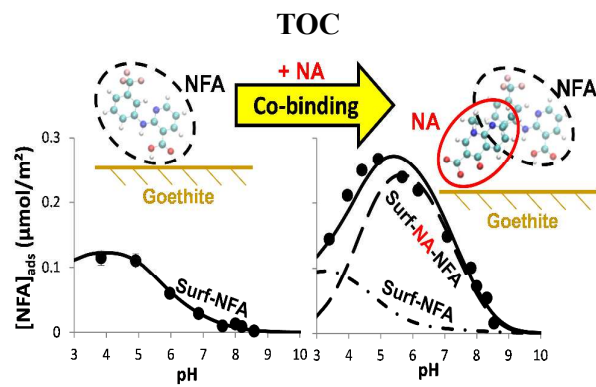
Figure 1



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Figure 2

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