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Co-binding of pharmaceutical compounds at mineral surfaces: Molecular investigations of dimer formation at goethite/water interfaces

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1 **Co-binding of pharmaceutical compounds at mineral**
2 **surfaces: Molecular investigations of dimer formation at**
3 **goethite/water interfaces**

4
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23 **Abstract**

24

25 The emergence of antibiotic and anti-inflammatory agents in aquatic and
26 terrestrial systems is becoming a serious threat to human and animal health worldwide.
27 Because pharmaceutical compounds rarely exist individually in nature, interactions
28 between various compounds can have unforeseen effects on their binding to mineral
29 surfaces. This work demonstrates this important possibility for the case of two typical
30 antibiotic and anti-inflammatory agents (nalidixic acid (NA) and niflumic acid (NFA))
31 bound at goethite (α -FeOOH) used as a model mineral surface. Our multidisciplinary
32 study, which makes use of batch sorption experiments, vibration spectroscopy and
33 periodic density functional theory calculations, reveals enhanced binding of the
34 otherwise weakly bound NFA caused by unforeseen intermolecular interactions with
35 mineral-bound NA. This enhancement is ascribed to the formation of a NFA-NA dimer
36 whose energetically favoured formation (-0.5 eV compared to free molecules) is
37 predominantly driven by van der Waals interactions. A parallel set of efforts also
38 showed that no co-binding occurred with sulfamethoxazole (SMX) because of the lack
39 of molecular interactions with co-existing contaminants. As such, this article raises the
40 importance of recognising drug co-binding, and lack of co-binding, for predicting and
41 developing policies on the fate of complex mixtures of antibiotics and
42 anti-inflammatory agents in nature.

43 Introduction

44

45 Thousands of different emerging pharmaceutical contaminants occur in soils,
46 groundwater, surface waters as well as seawater from human and intensive farming
47 activities.^{1,2} Antibiotics and anti-inflammatory agents in terrestrial and aquatic
48 environments, in some instances at levels as high as several hundred ng per L³⁻⁶ are
49 posing detrimental ecological and health effects especially because of their growing use
50 in human and veterinary medicine. Because the fate of these compounds is often tied to
51 their affinities to surfaces of soil and sediment mineral particles^{7,8}, adsorption through
52 synergistic drug interactions is likely to become an emerging mechanism in
53 contaminated environments.

54 Although contaminants rarely exist in isolation, they often have been studied
55 individually with respect to sorption and/or complexation with naturally occurring
56 minerals.⁹⁻¹² Sorption of individual compounds to environmental surfaces involves
57 different mechanisms including metal bond, hydrogen bond, and van der Waals
58 interactions¹³. In multicomponent systems, co-existing contaminants can compete for
59 surface binding sites, or cooperatively bind by co-neutralisation of surface charge
60 and/or by direct molecular interactions. While competitive adsorption has been widely
61 investigated¹⁴⁻¹⁶, cooperative effects have been never reported for widely used
62 antibiotic and anti-inflammatory agents. In addition, because most traditional
63 environmental models are based on an individual contaminant basis, little is known on
64 their fate in mixed contaminant systems.

65 In this work, we assessed the ability of three typical antibiotic and
66 anti-inflammatory agents detected in affected environments^{6,17} (nalidixic acid (NA),
67 niflumic acid (NFA) and sulfamethoxazole (SMX)) to co-bind at minerals surfaces.
68 Goethite (α -FeOOH) is selected as model mineral because it is one of the most stable
69 thermodynamically iron oxyhydroxide at ambient temperature and the most abundant
70 one in natural settings. NA is a quinolone antibiotic that is widely used in humans and
71 animals and that typically co-occurs with SMX, a sulfonamide antibiotic commonly
72 used to treat a variety of bacterial infections¹⁸. Niflumic acid (NFA) is a non-steroidal
73 anti-inflammatory that is often used for rheumatoid arthritis.¹⁹ As will be detailed in
74 this work, investigations are mainly focused on NA and NFA as no co-binding effect are
75 typically observed with SMX. Vibration spectroscopic and density functional theory
76 (DFT) calculations of NA/NFA co-binding, as well as batch kinetic, pH-edges and
77 isotherms, were used to resolve uptake mechanisms of NA and NFA at goethite in
78 isolated vs. mixed systems. These efforts helped identify conditions under which drug
79 co-binding is likely to prevail in the environment.

80

81 **Experimental Methods**

82 **Materials and chemicals.** Nalidixic acid (NA), Niflumic acid (NFA),
83 Sulfamethoxazole (SMX), sodium chloride (NaCl), potassium hydroxide (KOH),
84 sodium hydroxide (NaOH) and hydrochloric acid (HCl) were obtained from Sigma
85 Aldrich, and were of analytical grade or better. The preparation and characteristics of
86 goethite are detailed in the supporting information (SI).

87 **Binding and co-binding experiments**

88 Kinetic adsorption experiments were conducted in 125 mL Nalgene bottles
89 containing 0.5 g/L goethite in 10 mM NaCl under an atmosphere of N₂(g). NA, NFA
90 and SMX concentrations were of 20 μM in both isolated (NA; NFA; SMX) and mixed
91 (NA+NFA; NA+SMX, NFA+SMX) systems. pH was adjusted using dilute NaOH or
92 HCl solutions to a pre-selected value. Aliquots were sampled during the course of the
93 experiments and filtered (0.2 μm) for analysis. Preliminary experiments showed that
94 adding the ligand simultaneously or sequentially after several hours of equilibration
95 had no significant effects on adsorption results.

96 Equilibrium adsorption experiments as a function of pH (4 < pH < 9) were
97 conducted in 15 mL polypropylene tubes under an atmosphere of N₂(g) to minimize
98 interferences with dissolved CO₂ at pH > 6.5 (Fig. S1). Adsorption isotherms were, in
99 turn, recorded at pH = 6 under N₂(g) for (i) equimolar concentrations of NA and NFA
100 (0.1 - 40 μM), (ii) [NA]_{tot} = 20 μM and varying [NFA]_{tot} (0.1 - 40 μM), and (iii)
101 [NFA]_{tot} = 20 μM and varying [NA]_{tot} (5 - 40 μM). The adsorbed amount was
102 calculated by depletion method. Desorption tests were also conducted at pH = 11 to
103 check the mass balance, and an average recovery of 99±2% for the investigated solutes
104 was obtained (see SI). Sorption and desorption experiments were performed at least
105 twice, and the reproducibility of the measurements was around 5% for NA and 10% for
106 NFA.

107 Aqueous concentrations of organic molecules were determined using a high
108 performance liquid chromatography (Waters 600 Controller) equipped with a

109 reversed-phase C18 column (250 mm×4.6 mm i.d., 5 μm) and a photodiode array
110 detector (Waters 996). The mobile phase was mixture of acetonitrile/water (60/40v/v)
111 contained 0.1% formic acid. The flow rate was set at 1 mL/min in isocratic mode. The
112 detector was set to 258 nm for NA, 283 nm for NFA and 270 nm SMX. All three
113 molecules could be analyzed with a single injection because they exhibited different
114 retention times (NA: 4.5 min; NFA: 10.1 min; SMX: 3.2 min).

115

116 **ATR-FTIR spectroscopy and MCR analysis**

117 Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectra were
118 recorded between in the 780-4000 cm⁻¹ region on an IS50 Nicolet spectrometer
119 equipped with a KBr beam splitter and a liquid nitrogen cooled MCT detector. A
120 nine-reflection diamond ATR accessory (DurasamplIR™, Sens IR Technologies) was
121 used for acquiring spectra of wet samples. The resolution of the single beam spectra
122 was 4 cm⁻¹.

123 Sample preparation for the ATR-FTIR analysis was the same as for batch sorption
124 experiments and has described in detail in our previous work²⁰. Spectra of goethite
125 suspensions in 10 mM NaCl were also taken in the absence of NA and NFA and then
126 subtracted from the spectra of sorbed NA and/or NFA in order to represent surface
127 complexes only. Two series of experiments were conducted at pH=6 in 10 mM NaCl for
128 0.5 g/L goethite and (i) 0 < [NFA]_{tot} < 100 μM with [NA]_{tot} = 100 μM or (ii) 0 <
129 [NA]_{tot} <100 μM with [NFA]_{tot} = 100 μM. Due to the relatively low solubility of both
130 NA and NFA (see SI), 1 M NaOH was used to dissolve NA or NFA to ensure a high

131 concentration (10 mM) for ATR-FTIR analysis of NA and NFA aqueous solution. The
132 solid form of NA and NFA was also analysed using ATR-FTIR by loading powder on
133 the crystal, and then a drop of water was added to apply it more uniformly. Additionally,
134 the effect of pH (4-6) on NA and NFA sorption to goethite in 10 mM NaCl was
135 investigated for $[\text{NA}]_{\text{tot}}$ or $[\text{NFA}]_{\text{tot}}=100 \mu\text{M}$ as described in supporting information
136 (SI).

137 Selected sets of ATR-FTIR spectra in the $1200\text{-}1700 \text{ cm}^{-1}$ region were then
138 analyzed by multivariate curve resolution (MCR) analysis²¹. These efforts extracted
139 spectral profiles and their relative concentrations (FTIR measurements cannot be used
140 to obtain absolute concentration values) of end-member components representing an
141 assemblage of the purest chemical species possible. Spectra sets were expressed in the
142 matrix \mathbf{A} (m rows of wavenumber and n columns of measurements), and offset to zero
143 absorbance at 1700 cm^{-1} , where absorption by the wet mineral pastes is constant. The
144 spectra were expressed in terms of a linear combination of spectral profiles ($\boldsymbol{\epsilon}$), akin to
145 molar absorption coefficients, and their concentration profiles (\mathbf{C}), and are related by
146 $\mathbf{A} = \boldsymbol{\epsilon}\mathbf{X}$ as in the Beer-Lambert law, such that that $\boldsymbol{\epsilon} \geq 0$ and $\mathbf{C} \geq 0$. Calculations of $\boldsymbol{\epsilon}$ and
147 \mathbf{C} were made with the MCR-ALS program²¹ in the computational environment of
148 MATLAB (The Mathworks, Inc.). No assumptions regarding the spectroscopic
149 responses of the different species are made through this process.

150

151

152

153 DFT Calculations

154 DFT+D calculations were performed using an ab initio plane-wave pseudopotential
155 approach as implemented in VASP.^{22,23} The Perdew-Burke-Ernzerhof (PBE)
156 functional²⁴ was chosen to perform the periodic DFT calculations using the projector
157 augmented-wave method (PAW)²⁵ and a cutoff of 400 eV. The dispersion forces were
158 taken into account using the Grimme D2 approach.²⁶ To avoid the heavier
159 computational treatment of magnetic and electron-correlated iron oxides, we chose to
160 perform DFT calculations on two Al oxy-hydroxides (non-magnetic compounds): (i)
161 diaspore (α -AlOOH) which is the Al(III) isomorph of goethite, and (ii) gibbsite (Al(OH)₃)
162 because the co-binding phenomenon is experimentally shown on this mineral surface
163 (See SI). This allowed also to perform more extensive calculations.

164 The bulk gibbsite and bulk diaspore were optimized and a (2x2) and a (4x4) cell was
165 chosen to build the basal surfaces, respectively. Then the molecules were optimized
166 separately in the same supercell as that used to model the surface, and the dimer was
167 also studied. Several protonation states of the NFA were considered. Since the
168 determination of adsorption free energy from water phase was not the aim of our study,
169 the solvent water molecules were not included in the calculations. The adsorption
170 energies computed here inform rather on the molecule-surface interaction strength. The
171 detailed calculation results are detailed in the SI.

172

173 **Results and Discussion**

174 **Macroscopic assessment of NA and NFA binding.** Binding kinetics of NA and NFA
175 in both single and binary systems followed pseudo-second-order kinetic model (Fig. S3)
176 and displayed comparable behaviours, with NA binding more strongly than NFA.
177 However, NFA loadings were considerably enhanced in the presence of NA, thus
178 providing a first line of evidence for synergetic intermolecular interactions at mineral
179 surfaces (SI). This can also be appreciated by ~4-fold slower adsorption rate of NFA in
180 the mixed system (pseudo-second order rate constant of $0.16 \text{ m}^2/\mu\text{mol}\cdot\text{min}$) than in the
181 isolated system ($0.60 \text{ m}^2/\mu\text{mol}\cdot\text{min}$). In contrast, mixed systems containing SMX did
182 not reveal any co-binding effects (Fig. S4).

183 NA and NFA binding at mineral surfaces in single system (Fig.1 for goethite)
184 follows the typical pH-dependent behaviour of carboxylic acids.^{10,27-29} NA adsorption
185 was accordingly greatest under acid to circumneutral pH, where goethite surfaces are
186 positively charged, and NA carboxylate groups deprotonated ($\text{pK}_a=6.19$ for NA at
187 infinite dilution³⁰, *cf.* Fig. S5). However, as NFA is a diprotic acid ($\text{pK}_{a1}=2.28$ and
188 $\text{pK}_{a2}=5.10$ at infinite dilution)³¹, it can exist as cationic, zwitterionic and anionic forms.
189 Only 23% of NFA was sorbed at acid pH and this percentage decreased with pH
190 increasing. Interestingly, binding of NA and NFA in mixed systems occurs over the
191 entire pH 4-9 range considered in this work (Figs. 1). This cooperative effect is more
192 pronounced for NFA because of its weaker adsorption in the isolated system (e.g.
193 increase of adsorption from 22% to 54% at pH 5). In addition, the pH-adsorption curve
194 of NFA (Fig.1b) becomes bell-shaped as in NA (Fig. 1a), suggesting that the NFA

195 binding to goethite surfaces in the binary system is closely related to the behavior of
196 NA binding.

197 Because this synergetic effect was observed for both molecules, two approaches
198 were adopted to study NFA and NA co-binding in mixed systems. Firstly, varying the
199 concentrations of NA and NFA, at ratio of 1:1 ($[NFA]_{tot} = [NA]_{tot}$), strongly points to
200 NA/NFA co-binding at goethite surfaces under a wide range of solute concentration
201 (0.1 to 40 μM), a range that notably partially overlaps with those in aquatic
202 environments (nM to several dozens of nM)³⁻⁶ (Fig. 2a). Indeed, NFA and NA loadings
203 at pH 6 in isolated systems were lower than those measured in equimolar mixtures (Fig.
204 2a). Interestingly, by plotting the NFA loadings versus NA loadings in equimolar
205 mixtures, an excellent linear correlation was obtained (Fig. 2b, $[NFA]_{ads} = 0.6344$
206 $[NA]_{ads}$, $R^2 = 0.999$, fitted line was not shown). Secondly, varying $[NA]_{tot}$ at constant
207 $[NFA]_{tot}$ (20 μM) and, conversely, varying $[NFA]_{tot}$ at constant $[NA]_{tot}$ (20 μM) showed
208 that increasing surface loadings of one ligand increases the other. However, a plateau
209 was reached for $[NFA]_{ads}$ where $[NA]_{tot}$ varies, which is likely to have arisen from
210 molecular layers acting as steric or electrostatic barriers preventing additional
211 binding.³²

212

213 **Molecular investigations of co-binding.** Vibration spectroscopy and density
214 functional theory (DFT) calculations were used to provide clues on the mechanisms
215 through which NA and NFA bind and co-bind at goethite surfaces. We note that DFT
216 calculations were performed on diaspore (Fig. 3), which is the Al(III) isomorph of

217 goethite, to avoid the otherwise heavier computational treatment of magnetic and
218 electron-correlated iron oxides. The (110) face was chosen to emulate the dominant
219 crystallographic face of the goethite particles under study.

220

221 The fingerprint region of these molecules ($1200\text{-}1800\text{ cm}^{-1}$; Fig. 4, see also band
222 assignments in SI) showed a 25 cm^{-1} blue shifts in C-O stretching modes (ν_{COO}), while
223 no obvious shift for the ring modes ν_{ring} was observed. This suggests direct interactions
224 of carboxyl groups with goethite but little interaction with the aromatic and pyridine
225 rings during the sorption of NA and NFA in single system^{13,33}. Though vibration
226 spectroscopy suggests both metal- and hydrogen-bonding for NA, DFT calculations
227 suggest that hydrogen bonding is the preferred binding mode for NA (-0.34 eV vs.
228 $+0.44\text{ eV}$ for inner sphere complexation) and that it is 0.37 eV more favourable than
229 NFA ($+0.03\text{ eV}$). Thus while both complexes are stabilised by direct hydrogen bonds
230 between carboxyl groups and surface hydroxo groups, NA binding is made stronger by
231 a vicinal carbonyl of the pyridine ring and involves a hydrogen-bond cycle between the
232 molecule and two surface water molecules (Fig.3). In contrast, this cycle is not only
233 absent in NFA but when we forcefully hydrogen bonded NFA with an adsorbed water
234 simulations showed that this water reoriented itself towards a neighboring water
235 molecule. The weak nature of NFA binding can even be compared to those of
236 monocarboxylic acids (*e.g.* acetate or benzoate¹³).

237

238 Vibration spectra of mixed NA+NFA systems exposed to goethite (Fig. 4) showed
239 that increasing NFA concentrations (0, 10, 20, 50 and 100 μM) with $[\text{NA}]_{\text{tot}} = 100 \mu\text{M}$
240 systematically increased the intensities of the characteristic bands of NFA
241 ($\nu_{\text{COO,as}}=1480\text{-}1560 \text{ cm}^{-1}$), yet the resulting spectra cannot be represented as simple
242 linear combinations of the isolated goethite-NA and goethite-NFA systems (Fig. S7a).
243 For instance, the ring mode ($\nu_{\text{C=C,ring}}$) of NA was shifted from 1578 cm^{-1} to 1522 cm^{-1}
244 and that of NFA was split into two bands (1335 and 1348 cm^{-1}) suggesting perturbation
245 of C-C stretches and/or C-H bends of the aromatic and pyridine rings^{34,35}, and thus
246 formation of dimer involving the aromatic and pyridine rings of NFA and NA. These
247 observations also hold for the converse experiments where NA concentrations (0, 10,
248 20, 50 and $100 \mu\text{M}$) are increased with $[\text{NA}]_{\text{tot}} = 100 \mu\text{M}$ (Fig. S7b).

249 A multivariate curve resolution (MCR) analysis²¹ of these spectral sets provided
250 further insight into the nature of NFA and NA co-binding. MCR decomposed each
251 spectral sets into two separate spectral components (Figs. 5 a,b) representing the purest
252 extractable mineral-bound NFA and NA complexes (MCR I) and those under
253 competing systems (MCR II). The related concentration profiles (Fig. 5c) revealed that
254 addition of NA to mineral-bound NFA was more effective at altering the spectral
255 profile of NFA than the converse addition of NFA to mineral-bound NA. Still, as the
256 resulting MCR II components are markedly similar, our results suggest that the
257 resulting surface complexes at equimolar NA and NFA levels are strongly similar
258 irrespective of the order of addition. Finally, we note that these observations also hold
259 for lower concentrations (Fig. S8 where $[\text{NA}]_{\text{tot}} = 20 \mu\text{M}$ and $[\text{NFA}]_{\text{tot}}=10\text{-}40 \mu\text{M}$).

260 In line with the concept that NA enhances NFA binding, DFT calculations reveal
261 that NFA binding to a hydrogen-bound NA on diaspore is energetically favourable
262 (-0.21 eV). The resulting dimer formed via favourable hydrogen bonding and van der
263 Waals interactions by -0.50 eV, and the two COOH moieties of this dimer are parallel
264 with one another thus increasing the strengths of its interactions with mineral surfaces
265 (*cf.* SI for more information and Figures S10-S15). As such, recalling that NA binding
266 is favourable by -0.34 eV, binding of NFA to a pre-sorbed NA should be favourable by
267 -0.55 eV. In comparison, NA and NFA binding at different locations on the same
268 diaspore surface are favourable by only -0.30 eV and the formation an unbound
269 NA/NFA dimer is favourable by -0.50 eV.

270

271 Because the main mode of attachment for NA is achieved via hydrogen bonding at
272 circumneutral conditions, this phenomenon is not only limited to strongly reactive
273 faces of minerals, such as the (110) face of goethite/diaspore or edges of clays, but also
274 on the basal planes of minerals. The planes are of widespread occurrence in platy metal
275 (oxy)(hydr)oxides as well as phyllosilicates (*e.g.* clays) and typically display (hydr)oxo
276 groups that are strongly resilient to ligand exchange, yet are active hydrogen bonding
277 sites. To illustrate this point further the SI contains further details on the energetics of
278 NA/NFA co-binding on the basal plane of gibbsite, an important aluminium hydroxide
279 in natural but also industrial settings. Gibbsite gives more weight to our demonstration,
280 since the NA/NFA co-binding is experimentally shown to occur on this mineral surface
281 (See Fig. S16).

282 Those results also fall precisely in line with those obtained for diaspore, and suggests
283 the possibility in generalizing our finding to an even broader range of minerals and
284 particles which capable of stabilizing NA-like molecules via hydrogen bonding. Our
285 calculations consequently lend strong independent support for the concept that NA and
286 NFA co-bind at mineral surfaces of even contrasting structure, and that a dimer-type
287 species stabilized by intermolecular hydrogen bonding and van der Waals interactions
288 could be responsible for this phenomenon.

289

290 **Implications for transport of pharmaceutical compounds in nature.** Our concerted
291 macroscopic and molecular efforts both provide evidence that NFA-NA interactions
292 mutually enhance binding at mineral surfaces such as goethite. This cooperative effect
293 is more pronounced for NFA because of its intrinsically weaker affinity for mineral
294 surfaces, and occurs under environmentally relevant conditions of drug concentration
295 and pH. Vibration spectroscopic data show that addition of NA effectively alters the
296 nature of mineral-NFA binding but that converse addition of NFA to mineral-bound
297 NA results in a less dramatic change in the nature of NA binding. In support to these
298 finding DFT calculations showed that NFA binding on mineral faces of even strongly
299 contrasting structures is thermodynamically favoured only when NA is pre-adsorbed
300 either metal-bonded or hydrogen-bonded. This favoured form of binding could be
301 explained by the formation of a NFA-NA dimer stabilised by hydrogen bonding and
302 van der Waals interactions. The lack of co-binding seen in SMX also suggests the

303 importance of understanding drug interactions in aqueous solutions, a finding that also
304 calls for new studies along these lines.

305 This study is the first to show that mineral-bound antibiotic molecules can be
306 specific adsorption sites for other antibiotic molecules, and that layered-like coatings
307 involving anti-inflammatory agents may even form at mineral surfaces. As water
308 resources are exposed to complex mixtures of chemicals³⁶, including natural organic
309 matter and metal ions, additional efforts resolving the underlying principles governing
310 cooperative sorption should be made to accurately assess the fate of co-existing
311 contaminants in the environment. This becomes even more so urgent under the growing
312 number aquatic ecosystems and groundwater systems exposed to emerging
313 contaminants including non-prescription drugs, antibiotics, hormones and prescription
314 drugs^{36,37}. As a result, recognising the importance of drug co-binding at mineral
315 surfaces, and the conditions where it does not occur such as in the case of SMX, is key
316 to the successful development of models for predicting the fate of these contaminants,
317 and for guiding policies on actions needed to mitigate this growing environmental
318 problem.

319

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325 **Supporting Information Available**

326 Details of the materials used in this study, mineral characterization, analytical and DFT
327 methods, and additional data are available in the Supporting Information. This
328 information is available free of charge via the Internet at <http://pubs.acs.org/>.

329

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435 **Figure captions**

436

437 **Figure 1.** Left: pH-adsorption edges of a) NA single ($[NA]_{tot} = 20 \mu M$) and binary
438 ($[NA]_{tot} = [NFA]_{tot} = 20 \mu M$) and b) NFA single ($[NFA]_{tot} = 20 \mu M$) and binary
439 ($[NFA]_{tot} = 20 \mu M$; $[NA]_{tot} = 10$ and $20 \mu M$) systems on goethite, with 10 mM NaCl.
440 Right: molecular structures of NA and NFA.

441 **Figure 2.** a) NA and NFA sorption to goethite for single systems (full symbols) and
442 binary system where $[NA]_{tot} = [NFA]_{tot}$ (empty symbols). NA and NFA concentrations
443 were varied from 0.1 to 40 μM . For the sake of readability, the behaviour at very low
444 concentrations was shown in the insert. b) $[NFA]_{ads}$ vs $[NA]_{ads}$ at three experimental
445 conditions: (i) varying both compounds from 0 to 40 μM (black), (ii) $[NFA]_{tot} = 20 \mu M$,
446 $0 < [NA]_{tot} < 40 \mu M$ (red), and (iii) $[NA]_{tot} = 20 \mu M$, $0 < [NFA]_{tot} < 40 \mu M$ (blue).

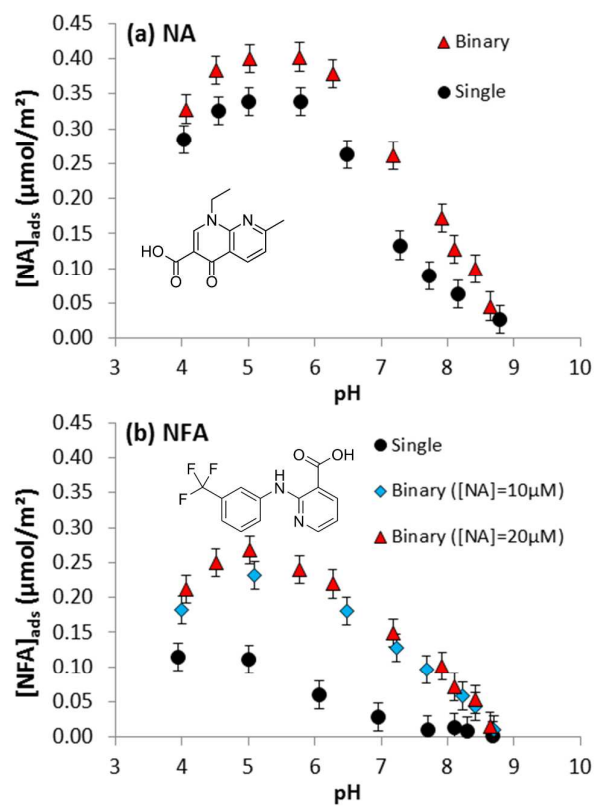
447 **Figure 3.** NA and NFA molecules co-adsorbed on the diaspore surface, with NA
448 adsorbed as (*left*) inner sphere ($E_{ads} (NFA/NA) = 0.07$ eV, athermic process) and (*right*)
449 outer sphere ($E_{ads} (NFA/NA) = -0.21$ eV). A negative energy indicates an exothermic
450 process.

451 **Figure 4.** ATR-FTIR spectroscopy on goethite. (a) from top to bottom: NA single
452 system, dissolved NA ($NA_{(aq)}$ in 1 M NaOH), NA-NFA binary system ($[NA]_{tot} = 100$
453 μM , $10 < [NFA]_{tot} < 100 \mu M$; the arrows show increasing $[NFA]_{tot}$), NFA single system,
454 dissolved NFA ($NFA_{(aq)}$ in 1 M NaOH). Bold and thin dashed lines show characteristic
455 bands of $NA_{(aq)}$ and $NFA_{(aq)}$, respectively. Numbers denote $[NFA]_{tot}$. Spectra were
456 normalized according to the band at 1448 cm^{-1} , since NA is the major component.

457 **Figure 5.** MCR-extracted spectral profiles from FTIR spectra of (a) 100 μm NFA + NA ,
458 (b) 100 μm NA + NFA, both including reference spectra, and (c) associated
459 concentration profiles corresponding to components MCR I and II. These concentration
460 profiles underscore the larger propensity of NA at displacing bound NFA, than NFA at
461 displacing NA.
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Figure 1

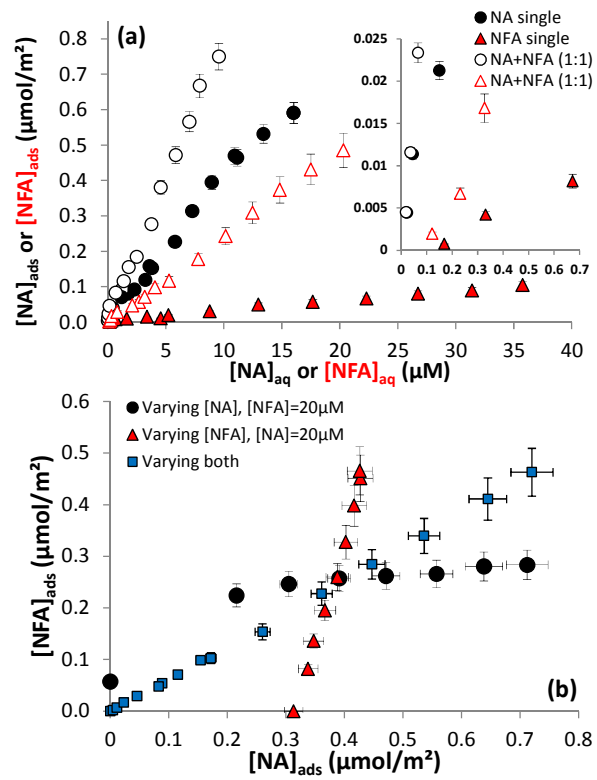


Figure 2

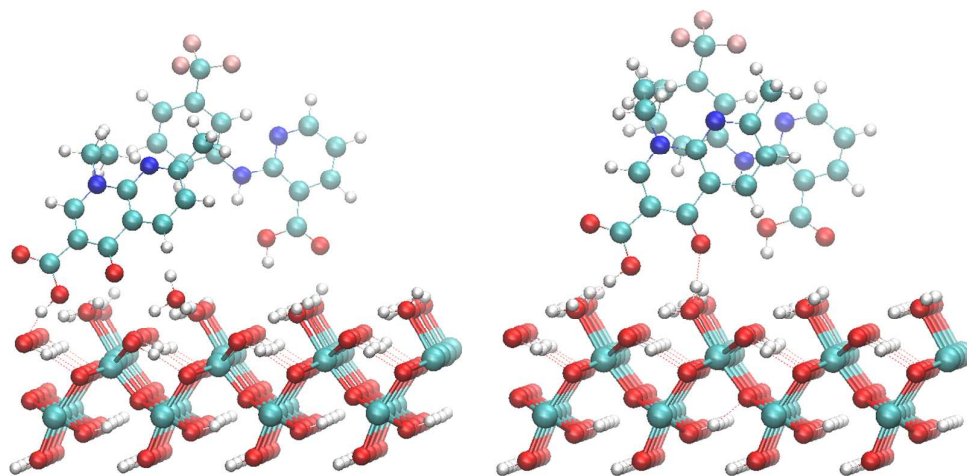
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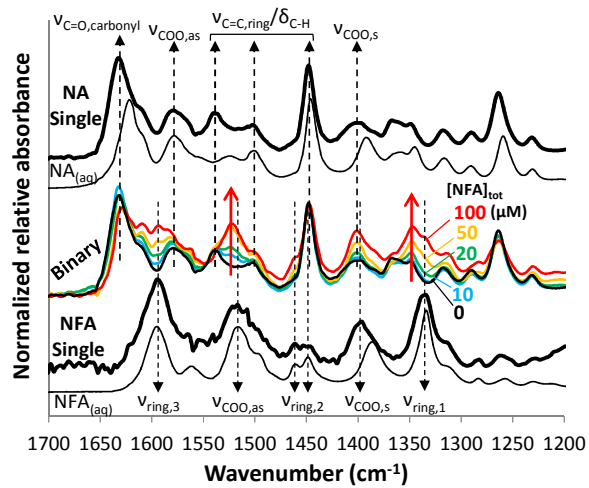


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Figure 3

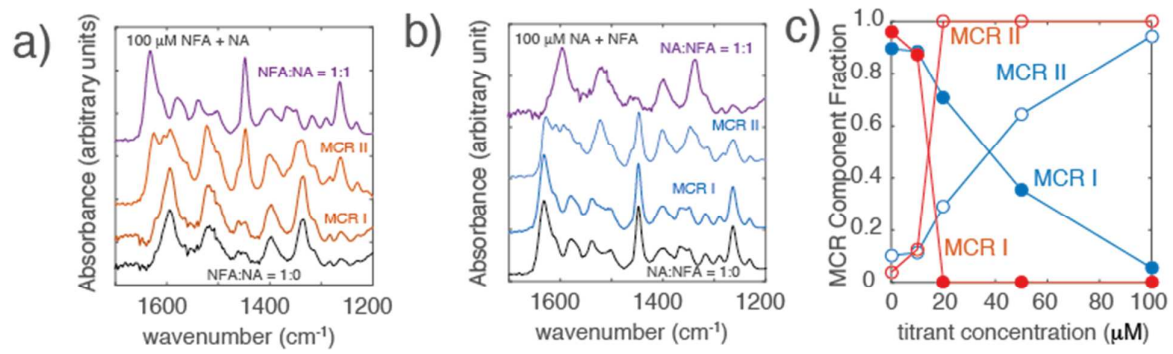


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Figure 4



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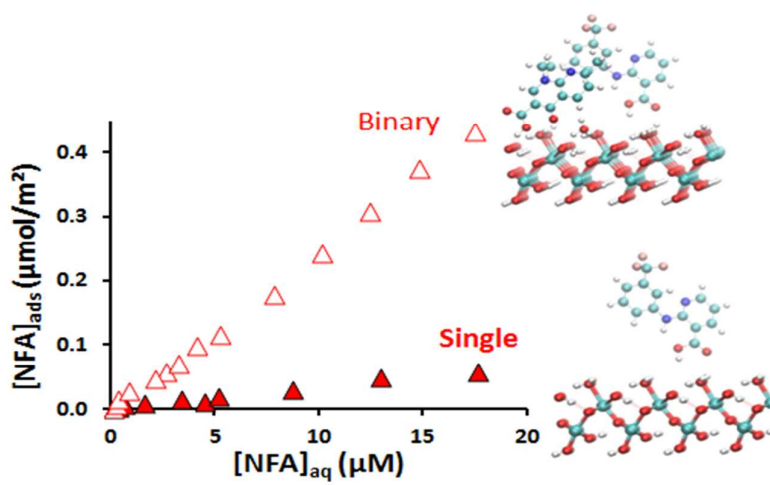
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Figure 5

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TOC

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