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Molecular Docking as a Tool to Examine Organic Cation Sorption to Organic Matter

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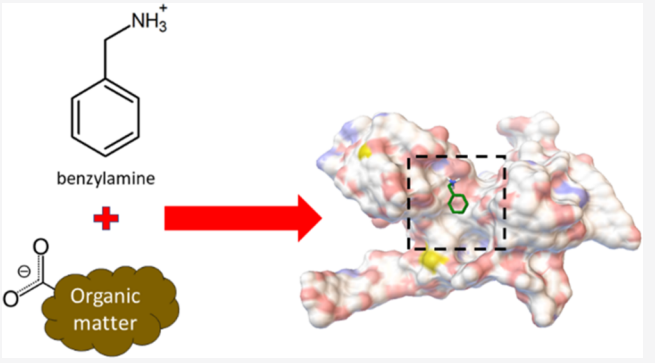
ABSTRACT: Molecular docking simulations were performed to examine the structural effects of organic cations on their sorption to organic matter. A set of benzylamine compounds was used to assess the sorption trends arising from the systematic structural differences between ring or nitrogen substituents. Binding simulations were performed using AutoDock 4.2 with Schulten's proposed soil organic matter as a representative organic matter structure. The calculated binding energies for the sorbate compounds correlated strongly with the measured sorption energies for Pahokee peat, indicating that the simulated binding energies and their associated sorbate orientations were representative of the experimental conditions. Graphical docking orientations showed primary, secondary, and tertiary aminium compounds to form hydrogen-bond interactions with deprotonated carboxylic acid groups in a pocket of the organic matter structure. Quaternary ammonium compounds formed pi−pi or cation−pi interactions with the aromatic groups elsewhere in the same organic matter pocket. Ring substituents showed no clear trends in sorption energies with the substituent group type for primary aminium compounds. Rather, substituent groups altered the simulated van der Waals, electrostatic, hydrogen-bond, and desolvation energy contributions to the overall sorption energies, in part because of the variations in docking orientations between compounds. Increasing methyl substitution of the aminium nitrogen group was associated with an increase in van der Waals energy contributions and a decrease in electrostatic energy contributions to the overall compound sorption energies because of aminium charge delocalization into methyl substituents and steric hindrance from methyl substituents to form specific interactions. The findings illustrate how molecular docking can be used to explore the effects of organic cation structure on sorption interactions with organic matter.



KEYWORDS: *binding, organic matter, cation, modeling, molecular docking*

INTRODUCTION

A key component to the fate and bioavailability of cationic organic contaminants (e.g., surfactants and pharmaceutical compounds) in the environment is the extent of sorption to the carbon-based organic matter component of environmental solids.[1−3] The extent to which compounds sorb to organic matter from the water phase can be expressed through the sorption coefficient, K_d (L kg^{-1}), that gives the ratio of the sorbed concentration, C_s (mass kg^{-1}), to the dissolved phase concentration, C_w (mass L^{-1}), at equilibrium:[4]

$$K_d = \frac{C_s}{C_w} = \exp\left(-\frac{\Delta G_{sorb}}{RT}\right) \quad (1)$$

where ΔG_{sorb} (kcal mol^{-1}) is the free energy of sorption. Knowledge of K_d values is essential for performing comprehensive risk assessments for environmental contaminants in order to estimate chemical distributions and exposures.[5] Available predictive tools for calculating K_d values for organic matter components were developed using sorption data from nonpolar organic contaminants and do not account for electrostatic interactions between positively charged organic cation compounds and negatively charged organic matter.[6] Parallel tool development for predicting the K_d values of cationic environmental organic contaminants has not matured to the same extent as that for their nonionic counterparts.[1] In response, Droge et al.[1,7] undertook a comprehensive study of organic cation sorption to organic matter by which they developed an empirical organic cation/organic matter sorption model that used aminium order to account for electrostatic charge contributions to sorption and McGowan volume model descriptors to account for nonionic

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contributions to sorption, namely compound size with polarity corrections. The model is successful in describing organic cation sorption to organic matter in the aggregate; however, further steps are necessary to address the coupled effects of changes in the sorbate molecular structure on both electrostatic and steric contributions to sorption.[3,8] The importance of coupled structure effects has long been known in the binding of charged organic drug compounds to enzymes.[9] This phenomenon has been demonstrated in the case of the analogous environmental situation of organic cation sorption to negatively charged aluminosilicate clay sites.[10] Thus, there is a need to develop modeling tools for organic cation sorption that account for the coupled effects of electrostatic interactions and steric contributions of compound structures when estimating K_d values for organic matter.

Computational chemistry tools offer the ability to use atomistic representations of entire molecular structures to model binding interactions between a sorbate and a sorbent. Molecular modeling methods are commonly applied in biochemistry to gain insight to specific intermolecular binding mechanisms (e.g., van der Waals interactions, electrostatic interactions, and hydrogen bonding) and to perform sorption free-energy calculations from these interactions. Computational approaches range in complexity from rapid docking tools to computationally intensive all-atom molecular dynamics simulations.[9,11] The force fields underlying these molecular modeling tools are well vetted and parameterized to describe the local atomic environments in organic structures and thus have potential for application outside of the biochemistry realm to examine organic cation binding to organic matter.[10,12] To date, computational studies of sorbate organic matter binding have largely focused on the identification of specific sorbate binding interactions for neutral contaminants with limited application to studying organic cation structural effects on binding.[13−16] Molecular dynamics simulations of polar and charged compound binding to representative organic matter structures have illustrated the significance of hydrogen-bond formation for directed compound interaction with organic matter functional sites, in conjunction with stabilizing hydrophobic and electrostatic interactions.[17,18] Molecular dynamics simulations of small organic compounds binding to a representative leonardite humic acid structure demonstrated strong correlations between the measured and calculated binding energies, illustrating the potential application of computational tools to calculate sorption energies.[19] A primary limitation to broader practical applications of molecular dynamics simulations is the computational costs associated with exploring sorption interactions for many different sorbate structures.[20,21]

Molecular docking methods offer a balance between detailed atomistic representations of the compound binding process and computational costs, which are much lower (hours) compared to molecular dynamics (days).[22−24] Docking is commonly used in the pharmaceutical sciences during drug development to screen optimal drug candidate structures for binding to known protein receptor sites.[25−27] As such, molecular docking tools can be used to calculate binding energies and binding orientations for large sets of sorbate structures. Binding energies are determined through pairwise atomistic interaction energy calculations of docked structures, using similar theory as for molecular dynamics simulations. Docking search algorithms identify energetically favorable binding orientations through the application of an empirical free-energy scoring function to calculate binding energies, offering computational cost savings over dynamic simulations.[22,28,29] Iterative convergence criteria are used to identify low-energy binding orientations of the bound sorbate−sorbent complex.[30] Additional computational cost gains are obtained by fixing the sorbent structure to be rigid throughout the docking simulation, thereby minimizing the number of calculations performed, compared to all-atom molecular dynamics simulations.[11] Sorbent structures are initialized in the docking routines for drug discovery using experimental crystallography data of protein structures that are readily available (e.g., Protein Data Bank: www.rcsb.org). In contrast, the extension of molecular docking to organic matter does require first a representative organic matter structure to perform meaningful molecular docking simulations of sorbate binding to organic matter.

Experimental characterization of various organic matter materials has allowed the development of atomistic organic matter representations for implementation in molecular modeling.[31−34] Schulten et al. proposed a conceptual humic acid structure based upon major organic matter fragments characterized through various spectroscopic and analytical pyrolysis techniques.[33,35,36] The structure has since been used to develop a three-dimensional soil organic matter (SOM) structure that includes bound proteinaceous (hexapeptide AspGlyArgGluAlaLys) and saccharide structures (cellulose subunit). We note that the use of a macromolecule to represent SOM instead of small OM fragments is not without dissent.[37] The humic acid fraction of the Schulten SOM structure includes characteristic humic acid subunits with intramolecular hydrogen bonds.[38] The "Schulten humic acid" structure has been applied in various molecular modeling studies to elucidate contaminant binding interactions to organic matter.[14,16,39,40] To our knowledge, the Schulten SOM structure has yet to be implemented systematically in the molecular docking studies of organic matter binding for a suite of organic cations to explore the structural effects to sorption. An optimized 3D version of the fully solvated Schulten SOM structure is widely accessible for use from the "The Virtual Museum of Minerals and Molecules" for exploratory computational simulations and is used herein for proof of concept.[41]

The purpose of this study was to assess whether molecular docking tools can be used to gain insights into organic cation structural effects on sorption to organic matter. Docking simulations used the Schulten SOM structure and were performed for a set of benzylamine derivatives and substructures with systematic structural differences through either ring substitutions or aminium nitrogen methylation (Table S1). Tested structures were purposefully chosen to allow for the evaluation of cation size, polarity, and aminium charge distribution effects on sorption (Figure S1)[42−44] These compounds have been used previously to examine the cation structure effects on aluminosilicate clay sorption.[44] Graphical docking outputs were used to examine cation structural effects on the underlying sorption mechanisms. Comparisons of simulated sorption energies to the experimental measurements of cation sorption energies with Pahokee peat were used to evaluate the representativeness of docking outputs. The optimized docking protocol was extended to a set of pharmaceutical cations possessing multiple rotatable bonds and/or polar moieties to examine the docking performance for structurally complex sorbate compounds that demonstrate a range of potential binding orientations.

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MATERIALS AND METHODS

Sorbents and Chemicals. Bulk Pahokee peat (1BS103P, International Humic Substances Society) was used as the representative soil organic matter. The peat was filtered and sieved to achieve a particle size range of 0.7−25 μm to prevent sorbent particle losses from the column. Silicon carbide (SiC) from Alfa Aesar was filtered and sieved to obtain a particle size range of 0.75−74 μm. Sorbate compounds (Table S1) were obtained from Sigma-Aldrich and Acros Organics. Uracil was used as an unretained tracer to quantify travel times in the packed columns. All other chemicals were of ACS grade. All solutions were prepared in high-purity water from a MilliQ system (Waters).

Collection of Experimental Sorption Data. Column chromatography was used to obtain experimental sorption data for the tested structures with Pahokee peat.[42] Injected compound retention times were used to extract paired C_w and C_s values under conditions of varied compound mass injections so that sorption isotherms could be plotted. A Pahokee peat/inert SiC mixture was made in a 5:1000 ratio and packed into a 30 mm length, 2.1 mm inner diameter column (Restek #25118). A control column containing only SiC was used to account for potential sorption interactions with the SiC diluent. The columns were packed using a procedure outlined by Jolin et al.[42,45] and loaded onto an Agilent 1100 HPLC system with a UV−vis detector. Solutions were made with high-purity water from a MilliQ system (Waters), and all compound solutions were prepared directly in water, with concentrations ranging from 0.02 to 0.1 mM for isotherm measurements. Compounds were analyzed individually at a flow rate of 0.1 mL min^{-1} with a 5 mM $CaCl_2$ mobile phase at a pH of 6.8. All sorbates were detected at a wavelength of 210 nm. All compounds, including an unretained uracil tracer, were measured in triplicate at each injection concentration on both the SiC/peat and SiC columns. The zeroth moments of the chromatograms were used to validate reproducibility through mass balance which showed mass recoveries of 94−105%. The first moments of the chromatograms were used to obtain single-point K_d values for each injected compound concentration. The single-point K_d values were converted to the equivalent C_w, C_s pairs that were used to construct sorption isotherms to verify linearity. All K_d values were assumed to be in the linear range of the isotherm if two or more initial concentrations had similar K_d values (within 1 standard deviation of each other), and sorption coefficients were obtained from the slopes in the linear range of measured isotherms.[42]

Isothermal titration calorimetry (ITC) was used to measure heats of binding for evidence of specific interactions between the tested sorbates and the Pahokee peat sorbent.[46−48] Isotherm runs were performed for all benzylamine compounds using a Malvern MicroCal VP-ITC system. Pahokee peat was suspended in a 5 mM $CaCl_2$ solution and equilibrated for 24 h to ensure saturation of organic matter functional sites with Ca^{2+}, thereby replicating the column conditions for the sorption coefficient measurements. A total mass of 15 mg_C Pahokee peat was loaded into the 1.4 mL Malvern sample cell. The control cell was filled with high-purity water from a MilliQ system. Solutions of the benzylamine compounds (0.02−0.1 mM) were used individually as titrants for fresh Pahokee peat suspensions. An amount of 300 μL of titrant was added to the sample cell in increments of 10 μL for a total of 30 injections with a 180 s delay between injections. The temperatures of the sample and control cells were maintained at 25 °C, and a stirring speed of 500 rpm was used to keep Pahokee peat particles in suspension. Origin 6.0 software was used to obtain enthalpies of sorption (kcal mol^{-1}) from isotherm curve fitting, assuming a single-site sorption model (model used to fit S-shaped isotherms). Independent measures of the free energy of sorption were obtained from the measured sorption coefficients and used with calorimetry-derived enthalpies to calculate the entropies of sorption.

Molecular Docking Simulations. Molecular docking simulations for each of the test cation compounds were performed in AutoDock 4.2[49] using the Schulten SOM structure (Figure S2). Atomic coordinate and bond connectivity information for the cation structures were obtained through PubChem. Energetically optimized bond length and atomic coordinate information for the cation structures were determined through gas-phase energy optimization with density functional theory (DFT) calculations at the B3LYP/6-31G* level of theory in Gaussian 16.[50,51] Atomic coordinate and bond information for the Schulten SOM structure were obtained from "The Virtual Museum of Minerals and Molecules".[41] Comparison of elemental composition and functionality shows that the Schulten SOM has similarities to Pahokee peat (Table S2). The SOM structure was optimized elsewhere in a hydrated state with explicit water molecules through molecular mechanics calculations using the software HyperChem.[35,52] The optimized conformation of the hydrated SOM structure was used as the input sorbent structure in AutoDock 4.2, and the molecular structure was held rigid through all simulations. All explicit waters were removed for the docking procedure to avoid the introduction of forced unfavorable cation−water interactions. Protonation of the Schulten SOM functional sites reflected environmental conditions (pH 6−8) with deprotonated carboxylic acid groups and protonated phenolic sites. Partial charges for cationic and SOM atoms were assigned using the default Gasteiger charge scheme in the AutoDock 4.2 software. The accuracy of the partial charge scheme was confirmed by conducting energy optimizations for the organic cations using the more commonly applied DFT in Gaussian 16 at the B3LYP/6-31G* level of theory.[51]

Autodock 4.2 uses a Lamarckian genetic algorithm with free-energy scoring from an empirically derived force field to search for, and converge on, a low-energy binding state between the sorbate and sorbent.[53] Individual simulation runs begin with an initial population of random docking orientations spanning the entire three-dimensional search space. Each run generates possible binding orientations through perturbations to the sorbate location and geometry to explore the search space. As new populations of sorbate binding orientations are generated, local energy evaluations are also performed to optimize binding cation geometries. In this study, simulation runs were bound with a maximum of 27,000 binding orientation generations and 2,500,000 energy evaluations using an initial population of 150 starting orientations. The lowest energy binding orientation of each run was carried over into the next simulation run as an initial orientation. A crossover rate of 0.8 and a mutation rate of 0.02 were used to introduce perturbations to sorbate geometries using a Cauchy probability distribution. To optimize local sorbate geometries throughout the simulation, local conformational searches were performed using a 6% probability that a local search would occur for a

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given run. Each run produces coordinate information for one low-energy binding orientation. In addition to the orientation of the sorbate compound in its bound state, the output files contain contributions of the individual binding interactions to the overall binding energy:[54]

$$E = W_{\mathrm{vdW}}\sum_{i,j}\left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + W_{\mathrm{hbond}}\sum_{i,j}E(t)\left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}\right) + W_{\mathrm{elec}}\sum_{i,j}\frac{q_i q_j}{\varepsilon(r_{ij})r_{ij}} + W_{\mathrm{sol}}\sum_{i,j}(S_i V_j + S_j V_i)\mathrm{e}^{-r_{ij}^2/2\sigma^2} \quad (2)$$

where the energy contribution of each interaction type to the total binding energy (E) is scaled according to empirically derived weighting factors (W_x) calibrated to experimentally determined binding poses and free energies for protein−ligand complexes.[55] All energy contributions utilize the summed pairwise calculations between the sorbate (i) and sorbent (j) atoms separated by a distance r_{ij}. The van der Waals (vdW) energy term is based on the 6/12 Lennard-Jones potential, where the depth of the energy well is defined using the atomic pair parameters A and B derived from the molecular dynamics AMBER force field, which is parameterized to simulate interactions between small organic molecules and biomolecules.[56] The hydrogen bond (hbond) term is based on a 10/12 potential, where C and D are the calculated parameters used to set the known maximum potential well depths for hydrogen acceptor/donor pairs. Hydrogen-bond strengths are also affected by hydrogen-bond directionality ($E(t)$). Electrostatic interaction energy (elec) is described by Coulomb's law using atomic partial charges (q) and a dielectric constant of bulk water (ε). Desolvation (sol) energy for a sorbate is calculated by the volume (V) of sorbent atoms surrounding the bound sorbate weighted by an exponential distance term (σ = 3.5 Å) to determine the percentage of the volume surrounding the sorbate atoms occupied by water upon docking. The percentage occupied is weighted using charge-based atomic solvation parameters (S) to determine total ligand desolvation energies.[54]

Blind docking simulations were performed first for the organic cations to explore favorable binding sites on the Schulten SOM structure. First, simulations were unconstrained such that all molecules could bind to any site across the entire Schulten structure. Then, further simulations enhanced the resolution of binding energy calculations by constraining the docking to only allow sorbate molecules to bind to the SOM region or pocket most frequently populated in the unconstrained simulation. The blind docking search space included the entire Schulten SOM structure using a grid box with 40 × 40 × 40 grid points (coordinate center of −15.389 × 24.667 × −0.667) and a grid spacing of 1 Å. During the blind docking procedure, a unique SOM pocket was identified within which all simulated cations would bind in the lowest energy state. Focused binding simulations were then performed using a grid box centered on the binding pocket (coordinate center, −15.311 × 28.056 × 1.445) and (12 × 16 × 16) grid points with a 1 Å grid spacing to determine energetically optimal sorbate binding conformations. This approach ensured solution convergence on an energy minimum before exceeding the limits on the maximum number of conformation and energy evaluations.

Each simulation of sorbate binding to the sorbent requires multiple runs to be initiated because the random perturbations between generations of the Lamarckian genetic algorithm yields different output orientations and associated binding energies for each simulation run. Increasing the number of runs in each simulation ensures a more thorough exploration of the sorbent topology to determine the most likely sorbate binding orientation. To assess the appropriate software settings such that these simulations would converge to the most likely sorbate binding orientation between organic cation sorbates and the organic matter sorbent, simulations were repeated for each sorbate by increasing the number of runs, with 10, 50, or 200 within a single simulation.

Cluster analyses were used to sort docking simulation output structures into unique binding orientations, based on geometrical similarity. Output orientations from each run in a simulation were ranked according to the root-mean-square deviation (RMSD) in sorbate conformation, compared to the initialized input sorbate structure. Orientations with sorbate conformations that showed RMSD to be within a tolerance of 1 Å of each other were grouped together in a single cluster. For 50- and 200-run simulations, a minimum of 10 runs was required to define a unique cluster. Calculated AutoDock 4.2 binding energies for each run were obtained by summing individual interactions without weighting (i.e., eq 2, W_x = 1). Binding energies within a cluster were averaged and compared to the measured sorption energies obtained from the experimental K_d values for Pahokee peat (eq 1).

RESULTS AND DISCUSSION

Measured Sorption Coefficients. Experimental measurements of sorption coefficients for the test sorbate compounds were used to benchmark the representativeness of docking calculations for physical systems. We note that the measured K_d values are specific for sorption to Pahokee peat with a 5 mM $CaCl_2$ background electrolyte at pH 6.8 (Table S3). We chose benzylamine as a reference compound because of the simplicity of its structure and the availability of compounds exhibiting systematic substitutions that have been shown to be important to compound sorption because they cause changes to the compound size and polarity (Figure S1). The K_d value of 69 L kg^{-1} for benzylamine was the lowest of the test primary aminium cation sorbate set. The importance of the cationic aminium group to Pahokee peat sorption was confirmed by the comparison of K_d values for benzylamine compounds with neutral aniline (K_d = 22 L kg^{-1}) and the net neutral zwitterion, 4-carboxybenzylamine (K_d = 17 L kg^{-1}); in the absence of a net positive charge, organic compounds similar in size and structure showed little sorption to Pahokee peat. The ring-substituted primary aminium compounds exhibited the highest sorption to the peat, with the measured K_d values ranging from 142 to 588 L kg^{-1} (Table 1, compounds 6−13). The highest K_d value was observed for naphthylmethylamine, which showed the impact of increasing the sorbate size without introducing a polar para-functional group. Among the other ring-substituted benzylamine compounds, there were no distinct trends observed between the electron-donating (e.g., CH_3) or −electron-withdrawing (Cl) nature of the ring substituents and the value of the sorption coefficients. *N*-Methyl-substituted aminium compounds (Table 1, compounds 1−5) showed lower sorption coefficients than ring-substituted primary aminium compounds, with K_d values ranging from 61 to 111 L kg^{-1}. Although these compounds show systematic

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Table 1. Experimental and Calculated Binding Energies[a]

		experimental	calculated
		K_d (L kg^{-1})	binding energy (kcal mol^{-1})
(1)	benzylamine	66	−7.60
(2)	*N*-benzylmethylamine	111	−7.60
(3)	*N*,*N*-dimethylbenzylamine	71	−7.64
(4)	benzyltrimethylammonium	61	−7.11
(5)	phenyltrimethylammonium	77	−7.14
(6)	2,4-dimethylbenzylamine	214	−8.65
(7)	2,4-dichlorobenzylamine	299	−8.79
(8)	naphthylmethylamine	588	−8.91
(9)	4-aminobenzylamine	142	−8.11
(10)	4-nitrobenzylamine	216	−8.32
(11)	4-trifluoromethylbenzylamine	148	−8.26
(12)	4-methoxybenzylamine	179	−8.28
(13)	4-aminomethylbenzoic acid	17	−6.04
(14)	aniline	22	−3.84
(15)	serotonin	571	−9.10
(16)	trimethoprim	491	−9.06
(17)	propranolol	735	−9.34
(18)	atenolol	82	−8.28
(19)	metoprolol	87	−8.67
(20)	diltiazem	279	−8.49
(21)	tramadol	42	−7.77

[a]Experimental sorption coefficients for the tested cations to Pahokee peat were determined using column chromatography. Experimental binding-free energies were calculated by converting the measured sorption coefficients (eq 1). Calculated AutoDock 4.2 interaction energy contributions were obtained for each sorbate by averaging the interaction energies obtained from the largest cluster in the simulation. Calculated binding-free energies for each sorbate were determined by summing the individual interaction energy contributions.

increases in size compared to benzylamine through the addition of methyl groups, the general trend of decreased sorption with increasing aminium methyl substitutions is consistent with the previous reports of organic cation sorption to organic matter due to the coupled structure effects on size and electrostatics.[1,7,57] Hence, insights into the sorption trends for benzylamine compounds were sought by utilizing computational tools in the form of docking simulations to conduct whole-atom simulations to understand how compound structure influences individual energy contributions (i.e., van der Waals, electrostatic, H-bonding, and desolvation) to the overall cation organic binding to organic matter.

AutoDock 4.2 Performance. Docking simulations were first performed in a search space encompassing the entire Schulten SOM molecule. This differs from the case of pharmaceutical sciences in which docking simulations are typically constrained to study compounds binding to a known, predefined protein receptor site. In the absence of such knowledge for organic matter, "blind" docking simulations were performed by including the entire sorbent molecule in the simulation search space to identify whether sorbate molecule dockings tended to converge to a unique location in the organic matter.[58−61] Indeed, output sorbate dockings converged to a common binding pocket within the organic matter structure for all tested compounds (i.e., the majority of dockings occurred at this site for all tested sorbates, Figure 1). The pocket consisted of a network of alkyl and aromatic carbon structures with ketone and quinone groups and

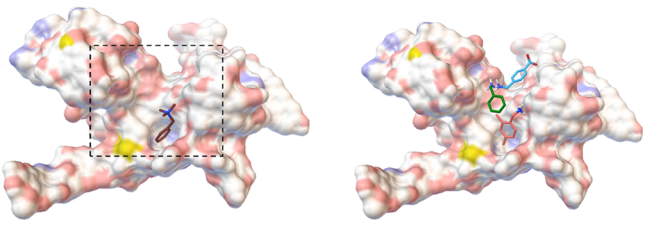

Figure 1. Schulten SOM molecule with AutoDockTools assigned with Goodsell polarity scheme (C—white, polar O—red, polar N—light blue, S—yellow, and H—same color as the atoms they are bonded to) showing the bound conformations obtained for individual test sorbates. Left: dotted square denotes the common binding pocket within which the lowest measured binding energy was observed for all tested cations, quaternary ammoniums docked oriented to form pi−pi (shown for benzyltrimethylamine in brown) or cation−pi interactions with the organic matter. Right: primary aminium compounds docked oriented to form hydrogen bonds with organic matter carboxylic groups, showing steric and polar effects from ring substituents impacted docking orientation and accessibility to organic matter carboxylic groups: benzylamine (green), 4-nitrobenzylamine (light blue), and 2,4-di-CH_3-benzylamine (pink).

deprotonated carboxylic groups accessible for the formation of specific electrostatic and hydrogen-bond interactions. This result was not intended to define a universal SOM binding site. Rather, this was the site to which most structure dockings converged; so, this was selected to maintain a consistent sorbent binding pocket while exploring the effects of sorbate structure changes on binding mechanisms. Docking simulations were then repeated in a search space constrained to the characterized binding pocket to determine the low-energy binding orientations of the test sorbates. Such an approach improves convergence to likely binding orientations of the sorbate by eliminating from the finite number of run calculations the portions of the organic matter structure with low probabilities of favorable binding energies. We note that the binding pocket is a much larger region that is often inferred through reference to "binding sites", particularly in the context of protein receptors that are specific to certain sorbent atoms. The algorithm search is focused on determining how compounds are spatially arranged when interacting with a binding site through the optimization of the free-energy score. As a result of using a constrained region of the sorbate structure in simulations, controlled exploration of compound structural effects on binding could be undertaken.

We used the docking simulations constrained to the identified Schulten SOM binding pocket to determine the number of runs necessary in a simulation to achieve convergence of conformational sampling. This was necessary, so that calculated binding energies could be compared to measured experimental values. First, the number of docking runs necessary to achieve a thorough sampling of the conformational space and to achieve a consistent convergence to low-energy binding orientations was evaluated. Increasing the number of docking runs from 10 to 200 in a simulation improved the convergence to identifiable low-energy binding orientations for all tested compounds (Figure S3). Ten simulation runs were not enough to achieve convergence of docking outputs to the same binding orientation, while the use of 200 simulation runs consistently allowed for clear convergence to similar binding orientations for each tested sorbate (Figure S3).

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As noted, binding orientations from the 200 simulation runs were organized using cluster analysis, based on the geometric similarity of the binding orientation. In some cases, the cluster that contained the largest number of geometrically similar binding orientations was not the cluster that contained the sorbate binding orientations with the lowest calculated energy of the simulation. For these situations, either the largest cluster that showed convergence to the same energy state the greatest number of times for all runs in the simulation or the cluster with the less frequently occurring and lowest absolute energy in the simulation could be the most representative binding orientation. Comparison of the simulation outputs against experimental data indicated that the average value of the binding energy from the cluster containing the largest number of simulation runs correlated best with the measured binding energies from experimental studies (Figure 2). The findings

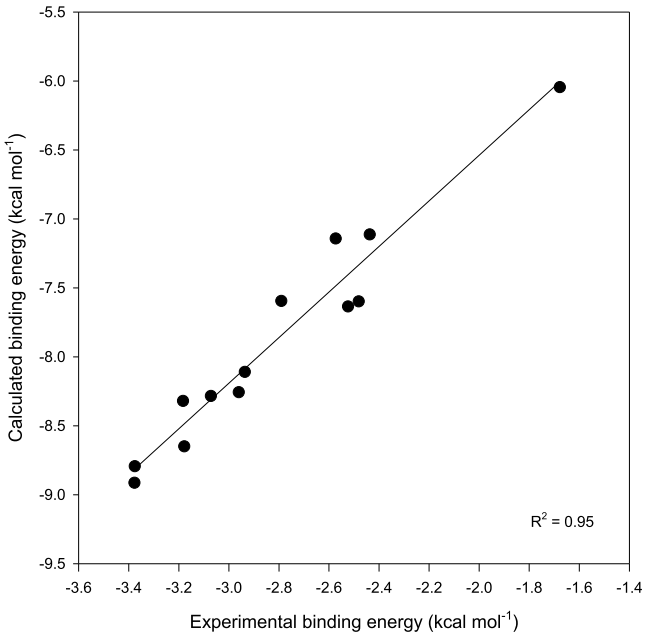

Figure 2. Correlation between the average binding energies of the AutoDock 4.2 output cluster containing the largest number of runs from a simulation with the experimental binding energy calculated from the K_d values for benzylamine and compounds with related structures sorbed to Pahokee peat. Data are for the cationic species of structures 1−13 in Table S1.

indicate that, for the AutoDock 4.2 search algorithm strategy, the probabilistic metric of the binding orientation to which runs in a simulation most frequently converged appeared to yield the most representative binding energy and, by inference, the most representative values for the individual intermolecular interaction energies that contribute to the binding orientation.

As is typically observed for computational chemistry simulations, the absolute values of the calculated binding energies differed from the measured values, here showing more negative values or stronger interactions than that observed experimentally. The relative energy differences ($\Delta\Delta G$) were not 1:1, with the correlation showing a slope of 0.57. This is in part due to the use of raw interaction energies that did not include empirical correctional interaction weighting factors to correct for interaction energy contributions toward the total binding energy (W_x = 1, eq 2). There is a need for additional experimental and docking work to propose interaction energy weighting factors to describe organic cation sorption to organic matter. Alignment of the simulations with our experimental Pahokee peat system (e.g., by obtaining weighting factors W_x, eq 2) was not undertaken as a part of this work, and further investigation is warranted. Nevertheless, we can draw several conclusions: (i) that the converged binding pockets of the Schulten SOM molecular model can be used as a proxy to explore the binding interactions to Pahokee peat sites for organic cation sorption under solutions of pH 6.8 with 5 mM $CaCl_2$; (ii) that the docking simulations show potential to yield estimates of sorption binding energies for organic cation sorbate interactions that correlate with experimental values, given the assumptions/decisions applied to the AutoDock 4.2 simulation parameters. These included assuming the organic matter structure remained rigid upon binding, no explicit water molecules were present near the binding site, and that Gasteiger charges appropriately describe partial charges on interacting molecules. We note that, although sorbent atom orientations were fixed spatially in the simulation runs, the specific sorbent atom orientations matched those obtained from molecular dynamics simulations of a fully solvated Schulten SOM structure.[52] Thus, we expect that local organic matter flexing in response to sorbate binding would be minimal, given the size of the simulated SOM binding pocket, relative to the sorbate compound sizes.

Benzylamine Structural Effects on Sorption Interactions. *Ring Substituents.* Graphical docking outputs were used for the initial examination of benzylamine ring substituent effects on sorbate binding orientations (Table 1—structures 1, 6−13). The reference compound benzylamine docked in an orientation showing hydrogen-bond formation between an aminium hydrogen and a carboxylic acid group in the organic matter binding pocket (Figure 1). In contrast, neutral aniline that lacks a charged aminium moiety docked with an orientation interaction with an aromatic group elsewhere in the organic matter binding pocket and with a separation distance consistent with a pi−pi bond interaction. Overall, the charged ring-substituted benzylamine compounds showed three different orientations in the binding pocket. Most ring-substituted compounds showed the same orientation as benzylamine with compounds oriented at the carboxylic acid group to maximize close contacts for stabilizing electrostatic and van der Waals interactions with the proximate organic matter atoms in the binding pocket. A second orientation was adopted by 4-nitrobenzylamine and 4-aminomethylbenzoic acid for which the aminium group participated in a hydrogen-bond interaction with the same carboxylic acid group as benzylamine; however, the molecules were oriented outward from the binding pocket (Figures 1 and S4), presumably to minimize unfavorable interactions between the organic matter carboxylic acid group and the electronegative para-substituents. A third orientation was observed for the 2,4-dimethyl- and the 2,4-dichloro-substituted benzylamine compounds which showed association with a different carboxylic acid group at a separate location in the organic matter binding pocket than that for benzylamine sorption (Figures 1 and S4). The presence of ortho-position substituents on these compounds appeared to cause a steric hindrance to bind at the carboxylic acid group that was most favored for the other ring-substituted benzylamine compounds, each of which had substitutions solely at the para-position. Taken together, the graphical simulations highlighted the importance of compound orientation contributions to the overall binding of benzylamine

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and related ring-substituted compounds, indicating that substituents do not strictly modify the size and polarity of compounds with a similar primary aminium group that might be anticipated to participate in binding interactions at the same sorbent site.

The influence of substituent effects on the calculated individual sorption energy contributions for ring-substituted benzylamine compounds showed no distinct trends (Figure 3).

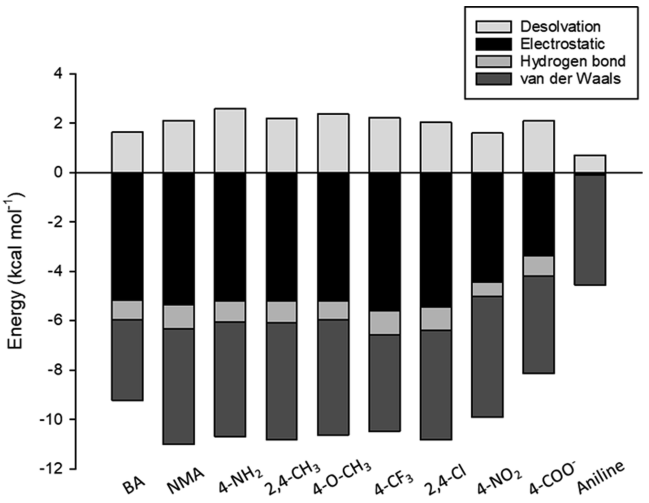

Figure 3. Total calculated binding energies of ring-substituted benzylamine compounds and neutral aniline, showing energy contributions from explicit van der Waals, electrostatic, and hydrogen-bond interactions and cation desolvation penalties. Abbreviations: benzylamine (BA), naphthylmethylamine (NMA), 4-aminobenzylamine (4-NH_2), 2,4-dimethylbenzylamine (2,4-di-CH_3), 4-methoxybenzylamine (4-*O*-CH_3), 4-(trifluoromethyl)benzylamine (4-CF_3), 2,4-dichlorobenzylamine (2,4-di-Cl), 4-nitrobenzylamine (4-NO_2), and 4-(aminomethyl)benzoic acid (4-COO−). Structures BA, NMA, 4-NH_2, 4-CF_3, and 4-OCH_3 docked to the same SOM carboxylic site; 4-COO^- and 4-NO_2 docked to the same carboxylic group, but para substituents were oriented away from the SOM pocket due to repulsion; 2,4-di-CH_3 and 2,4-di-Cl docked to a different carboxylic group in the SOM binding pocket.

One observable distinction was the absence of electrostatic or hydrogen-bond energy contributions to the overall binding energy for aniline, the neutral compound with structural similarities to the charged benzylamine compounds (Figure 3). Electrostatic energy contributions, including that from hydrogen-bond formation, accounted for the greatest fraction of the overall calculated binding energies for the charged primary aminium compounds. Electrostatic energy contributions were slightly smaller for 4-nitrobenzylamine and 4-aminobenzoic acid than the other compounds, indicating a contribution from the electronegative substituents in these compounds that was captured in the docking energy calculations. Across the ring-substituted benzylamine compound set, the calculated hydrogen-bond energies ranged from −0.589 to −0.985 kcal mol^{-1}. These slight variations in hydrogen-bond strengths suggested differences in hydrogen-bond angles arising from the differences in compound orientation discussed above (Figure S4). However, there were no clear trends between the calculated hydrogen-bond strengths and the three general sorbate orientations detailed above. For example, neither 4-nitrobenzylamine and 4-aminobenzoic acid nor 2,4-dimethyl- and 2,4-dichlorobenzylamine showed hydrogen-bond energy contributions that were distinctly different from that of other ring-substituted compounds (Figure 3).

Ring substituent effects on individual interaction energy contributions were not sufficiently large to dominate the trends in the overall sorption interactions. The presence of electron-withdrawing (e.g., CF_3) or electron-donating (e.g., NH_2) groups showed no clear trends in individual sorption energy contributions. Ring substituents increased the molecular surface area available to form stabilizing sorption interactions with organic matter atoms, and a weak positive correlation between the ring substituent volume and van der Waals energy contributions was observed. Substituent contributions to desolvation energies could only be compared for the four ring-substituted benzylamine compounds that docked in the same orientation (naphthylmethylamine, 4-amino-, 4-methoxy-, and 4-trifluoromethyl-benzylamine) because the AutoDock 4.2 strategy for calculating desolvation energy contributions considers compound size, polarity, and docking location. These four compounds showed no distinct trends between molecular volumes, dipoles, or polarizabilities and calculated desolvation penalties when the same SOM docking location was compared. Overall, these findings indicate that the compound structure effects on the cationic organic compound sorption to organic matter do not have the same additive contributions to the overall sorption energies as has been manifest for neutral organic compounds (e.g., basis for the classification tree, Figure S1).[13,62−64] Great care should be taken when predicting cationic binding affinities from the atom/fragment approaches developed for neutral compounds due to differences in the SOM binding locations and sorption mechanisms.

Nitrogen Methyl Substitutions. In contrast to ring substitution, methyl group substitution for hydrogens at the benzylamine nitrogen group did show consistent trends in energy contributions to the overall compound sorption to organic matter (Table 1—structures 1−5). First, the graphical outputs of energy-minimized binding interactions showed that substituents again influenced the orientation of the sorbed compound in the organic matter binding pocket. For benzylamine and *N*-methylbenzylamine, all 200 runs in the simulation showed the same carboxylic acid to be the compound location for binding in the organic matter pocket (Figure 1, benzylamine; Figure S5). Differences between the clustered runs within a simulation related primarily to the angle of orientation for the hydrogen bond donated from the sorbate aminium group to the deprotonated carboxylic acid group. The favored carboxylic acid group was also important for the binding of *N*,*N*-dimethylbenzylamine and served as the binding site for the cluster that contained the greatest number of run outputs in the simulation. However, not all of the 200 runs in the *N*,*N*-dimethylbenzylamine simulation yielded this location during the energy minimization algorithm. Some orientations showed *N*,*N*-dimethylbenzylamine association with aromatic carbon structures elsewhere in the binding pocket and in the vicinity of the benzyltrimethylamine compound location shown in Figure 1. The majority of the runs in the simulations for benzyltrimethylamine and the structurally related phenyltrimethylamine showed these compounds to bind in an orientation that allowed for pi−pi interactions between the sorbate ring structure and an alkylbenzene group in the binding pocket, as evidenced by the separation distances of 3.3−3.8 Å between the sorbate and sorbent molecules. In some cases, phenyltrimethylamine

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docked with an orientation to form a cation−pi interaction with the same aromatic group. Together, these trends suggest the importance of increased methylation at the aminium group to cause steric hindrance for the formation of hydrogen bonds with the deprotonated carboxylic acid group.

Increasing *N*-methylation of benzylamine compounds showed a shift in contributions to the overall binding energies from the electrostatic to van der Waals interactions (Figure 4).

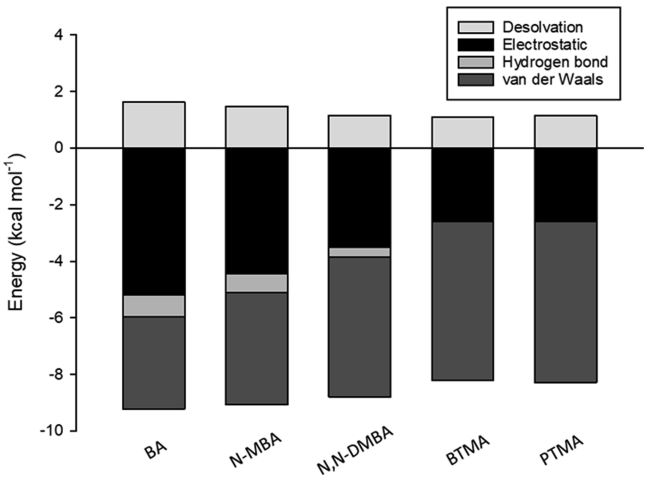

Figure 4. Total calculated binding energies of *N*-methyl-substituted benzylamine compounds and phenyltrimethylamine, showing energy contributions from explicit van der Waals, electrostatic, and hydrogen-bond interactions and cation desolvation penalties. Individual energy contributions show decreasing electrostatic sorption interactions with increasing aminium order arising from charge delocalization. Abbreviations: benzylamine (BA), *N*-benzylmethylamine (*N*-MBA), *N*,*N*-dimethylbenzylamine (*N*,*N*-DMBA), benzyltrimethylamine (BTMA), and phenyltrimethylamine (PTMA). BA, *N*-MBA, and some *N*,*N*-DMBA dockings docked to the same carboxylic group; BTMA, PTMA, and the majority of *N*,*N*-DMBA dockings docked oriented to form pi−pi or cation−pi interactions with an aromatic SOM group.

The energies of both electrostatic and hydrogen-bond interactions decreased from benzylamine to the quaternary ammonium compounds. Increases in the molecular volume from methyl substitutions is known to delocalize aminium positive charges over a larger aminium group surface area[10] which reduced the electrostatic sorption contributions. At the same time, the bulkiness of the aminium groups of *N*-methylbenzylamine and *N*,*N*-dimethylbenzylamine caused changes in the hydrogen-bond angle at the deprotonated carboxylic acid group site, leading to weaker hydrogen bonds in comparison to benzylamine (Figure S5). Both benzyltrimethylamine and phenyltrimethylamine lack hydrogen atoms to participate in hydrogen-bond interactions, and methyl substituents can sterically hinder the formation of specific interactions between the aminium nitrogen and organic matter. In parallel, desolvation energies for sorbate binding also showed a coupled reduction that was attributable to a lowered combined cost to desolvate the deprotonated carboxylic acid group and the aminium hydrogen. The increasing sorbate size with *N*-methyl substitution also showed an increased contribution of van der Waals interaction energies across the five compounds from benzylamine to the quaternary ammonium compounds (Figure 4). These findings illustrated that increasing aminium methyl substitution shifted the dominant sorption mechanism from electrostatic to van der Waals interactions with organic matter, such that the quaternary ammonium compounds interacted with the organic matter at the same binding site as the neutral compound, aniline.

Experimental Measures of Energy Contributions. Isothermal calorimetry measurements for select test benzylamine structures were used to provide additional experimental evidence in support of the AutoDock 4.2 simulated sorption mechanisms and formation of specific interactions (Figure S6). The weakly sorbing neutral aniline and zwitterionic 4-aminobenzoic acid did not have detectable heats of binding by fitting calorimetry data. The tested primary aminium ions showed the overall sorption energies to be dominated by enthalpic contributions, consistent with the formation of specific hydrogen bonds with organic matter sites. One exception was 4-nitrobenzylamine for which the binding energy was dominated by the entropic term, which may be due to resonance in the nitro group that prevents the formation of specific interactions. Ring substitutions to the benzylamine structure led to less favorable enthalpies compared to the parent structure due to the increased disruption of water−water interactions upon cavity formation from the increases in cation size. Heats of binding were also not detectable for *N*,*N*-dimethylbenzylamine or for the two quaternary ammonium compounds, validating the absence of specific hydrogen-bond formation, as indicated in the AutoDock 4.2 simulations. Further, the low enthalpic energy contribution to binding indicates the experimental sorption energies for these *N*-methyl-substituted compounds to be dominated by entropic contributions, which is consistent with the dominant contribution of van der Waals energies and the low extent of electrostatic energy contributions that were also indicated by the docking simulations. The findings provide evidence for the predicted docking orientations that demonstrate a shift in the role of electrostatic sorption from increasing aminium methyl substitutions. The tested low-order aminium ions were driven electrostatically to interact with the deprotonated carboxylic sites on the organic matter, whereas highly substituted aminium structures were hindered from forming specific interactions.

Extension to Pharmaceutical Cations. The docking procedure was extended to a set of pharmaceutical cations to evaluate the performance of this method for a group of compounds with more complex structures and more rotatable bonds (Table 1—structures 15−21; Table S4). Structurally complex compounds with rotatable bonds and polar groups demonstrate a range of possible binding conformations, making it difficult to identify orientations representative of physical systems. A minimum of 200 simulations were needed to achieve solution convergence to unique conformational clusters for the tested pharmaceuticals. Structures were first allowed to search the entire SOM structure for favorable binding orientations. The majority of dockings for all tested pharmaceuticals converged to the same organic matter binding pocket as above. Simulations were then constrained to the binding pocket to enhance the resolution of the binding energy calculations. As was the case for the smaller, rigid benzylamine compounds, average sorption energies for the cluster with the greatest proportion of runs in the simulation provided the best correlation with the experimental measures of sorption binding energies (Figure S7). All the tested pharmaceutical structures that included primary, secondary, and tertiary aminium groups

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showed docking orientations in which the charged aminium group formed a hydrogen bond with the organic matter carboxylic group favored by benzylamine (Figure S8). The sorbate structures oriented to maximize favorable interactions between the cation polar moieties and polar organic matter atoms. The findings indicate that a shift toward computational approaches may be possible to study the binding mechanisms for structurally complex cationic structures; this is a first step that must be further explored through the refinement of structural models and empirical calibration of the calculated binding energies.

Environmental Significance. This work highlights the promise of molecular docking tools to explore the sorption of cationic organic contaminants to organic matter. The strong correlation between the calculated sorption energies and the measured sorption coefficients indicated that the simulated binding orientations were representative of physical systems. Thermodynamic parameters from ITC measurements were also aligned with the simulated binding interactions, which demonstrate a shift in the role of electrostatic contributions to sorption with increasing aminium methyl substitutions. The results indicated that organic cation substituent effects are not strong enough to dominate individual sorption interactions, except in cases that substituents introduced steric hindrances directly at the charge binding site. Instead, the unique molecular structure and its associated unique electron distribution particular to the three-dimensional atomic arrangement of the sorbate necessitate adoption of molecular modeling techniques to capture the associated electrostatic interactions, hydrogen-bond formation, van der Waals interactions, and desolvation effects for charged organic species binding to organic matter. Molecular docking offers a computationally efficient approach to perform such atomistic calculations that consider the full range of unique sorption interactions for a given organic cation in conjunction with graphical outputs that help to explore the effects of the cation structure on the underlying sorption interactions. We note that the application of molecular docking approaches more broadly to include sorption of other neutral and anionic organic compounds and additional SOM structures will require parallel study approaches as the binding orientations and SOM sites are expected to differ, and thus trend lines herein are not transferable.

To take full advantage of the possible applications of molecular docking in environmental sorption applications, there is a need for further method refinement to improve the calculations of total sorption energies to achieve 1:1 correlations between the measured and calculated binding energies.[65] First, weighting factors in the binding scoring functions of the existing software tools were determined experimentally for protein−ligand interactions, and they are not directly translatable to calculate the accurate absolute interaction energies for organic matter. There is a need to determine the interaction energy weighting factors for the docking scoring functions to improve the search for low-energy binding orientations and to standardize the calculated total sorption energies that presently appear to overestimate sorption energies. Second, some improvements might be gained by developing SOM-specific force fields. While similar in the realm of biochemistry, SOM-specific force fields could yield improvement in the model predictive ability. Third, given the heterogeneous nature of organic matter and the distributed nature of sorbate orientations within the single SOM structure used herein, an approach that integrates a Boltzmann statistical representation of sorbate binding orientations across different SOM structural models[66] could better encapsulate ranges of likely binding energies. Additionally, the formation of organo-mineral complexes with clay minerals is likely to occur in physical systems.[67] Future structural models should aim to include both clay and organic matter structures to consider a more representative model for soil. Overall, molecular docking is a promising computational tool that can be used to gain insights into the underlying sorption mechanisms of organic cationic contaminants to SOM.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c06147.

Compound structures; structure selection rationale; experimental sorption coefficients and calculated binding energies; additional computational details; molecular docking graphical outputs; and ITC measurements (PDF)

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Notes

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