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Emerging investigator series: quantitative insights into the relationship between the concentrations and SERS intensities of neonicotinoids in water

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Environmental Significance Statement

A significant challenge in using surface-enhanced Raman spectroscopy (SERS) for quantitative analysis of neonicotinoids in water is the absence of a fundamental understanding of the relationship between their concentrations and the resulting SERS signals. This oversight has led to inconsistencies in the estimation of dynamic ranges and detection limits across different studies. Our study addresses this gap by delving into the adsorption thermodynamics of neonicotinoids on SERS substrates and illuminates its critical impact on the precision of SERS quantification of neonicotinoids. This study paves the way for the early detection of neonicotinoids in drinking water supplies that lack regular monitoring, such as private wells. This advancement can significantly reduce chronic human exposure to neonicotinoids and enhance protection of human health.

COMMUNICATION

Emerging investigator series: quantitative insights into the relationship between the concentrations and SERS intensities of neonicotinoids in water

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This study explores the theoretical foundation behind the application of surface-enhanced Raman spectroscopy (SERS) for neonicotinoid quantification. Our findings demonstrate that SERS intensities are determined by the thermodynamic adsorption behaviors of neonicotinoid molecules transitioning from aqueous phases to gold nanoparticle (AuNP) surfaces. The dynamic ranges and limits of detection can be accurately predicted by classic adsorption isotherms.

1. Introduction

Neonicotinoids are the most prevalent insecticides used in US agriculture, making up over 25% of global insecticide sales.[1] Recent years have seen growing concerns over their adverse impacts on ecosystems and humans.[2] For example, the EC50 of imidacloprid for *Daphnia magna* is 96.65 mg/L, leading to reduced population growth rates upon exposure.[3] While neonicotinoids are generally considered less toxic to mammals and humans, a rising body of research suggests that exposure may lead to various toxicities in humans, including effects on reproduction, hepatotoxicity, neurotoxicity, genotoxicity, and more.[4] The frequent occurrence of imidacloprid and clothianidin in both source and finished drinking water has raised concerns for their chronic human exposure.[5, 6] Liquid chromatography tandem mass spectrometry is the conventional method for neonicotinoid analysis in water.[7] Although extremely sensitive and accurate, this method is expensive and time-consuming, thus unlikely to fulfil the needs for large-scale neonicotinoid monitoring in drinking water supplies.

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Surface-enhanced Raman spectroscopy (SERS) provides an extraordinarily sensitive and rapid approach to detect water pollutants.[8, 9] SERS is the result of the substantially enhanced local electromagnetic field around plasmonic nanoparticles (PNPs) as their conduction electrons collectively oscillate under light excitation. Once the target analyte is positioned within nanoscale distance from plasmonic nanoparticle surfaces, its Raman scattering cross-section experiences an amplification approximately proportional to the fourth power of the local field enhancement factor.[10] Detection of single molecules via SERS has become increasingly common.[11, 12] With the improvement of SERS substrate uniformity and the application of internal standards, its application has been extended to the quantitative analysis of a broad range of organic chemicals.[13-15] Recently, SERS has been employed for the rapid pre-screening of neonicotinoids at low-part-per-billion levels in drinking water.[16]

Quantitative analysis of neonicotinoids in water via SERS still faces significant challenges. A key obstacle is the insufficient understanding of the relationship between neonicotinoid concentrations in water and their SERS intensities. To establish calibration curves essential for quantifying neonicotinoid in water, researchers typically graph the SERS intensities of neonicotinoids against either their initial (added) or logarithmic initial concentrations.[17, 18] The dynamic ranges of the calibration curves obtained vary substantially across different studies, with no overarching theory to account for these discrepancies. This absence of a unified explanation complicates the assessment of SERS's quantitative capabilities and the development of guidelines for future SERS-based analysis of neonicotinoids. In addition, the thermodynamically driven adsorption of neonicotinoids from the aqueous phase to PNP surfaces has typically been overlooked in these investigations.

In this study, we aim to bridge this knowledge gap by establishing a quantitative correlation between the SERS intensities of neonicotinoids and their thermodynamic adsorption behaviours on gold nanoparticles (AuNPs). Two of

the most widely used neonicotinoids, imidacloprid (IMD) and clothianidin (CLO), are selected as our primary analytes. To achieve adsorption equilibrium, a highly stable SERS substrate is immersed in imidacloprid and clothianidin solutions for an extended period. High-performance liquid chromatography (HPLC) is used to quantify neonicotinoid concentrations in aqueous phase before and after adsorption. This approach allows us to account for the concentration changes in the water, a factor often overlooked in previous research, indicating the amount of neonicotinoids adsorbed onto AuNPs. By correlating the SERS intensities with the initial, final, and differential concentrations in the aqueous phase, we develop a quantitative understanding of how the adsorption thermodynamics of neonicotinoids influence their SERS-based analysis. Distinct from prior research, our study uniquely incorporates the process of molecule adsorption from the aqueous phase to AuNP surfaces into the interpretation of neonicotinoid quantification data using SERS, establishing best practices for obtaining calibration curves. This study outlines a universal approach for predicting SERS quantification efficacy of neonicotinoids and provides insights in improving the quantification performance.

Methods

Preparation of SERS substrates

The bacterial cellulose (BC) used in this study was purchased from Cellulose Lab Inc. The gold nanoparticle/bacterial cellulose (AuNP/BC) SERS substrates were prepared using the method reported previously.[19] Initially, 12 pieces of BC (0.5 cm × 0.5 cm) were immersed in 0.7 mL of a 30 mM $HAuCl_4$ solution and vortexed for 30s. Subsequently, the BC pieces were transferred into 50 mL of boiling Na_3Cit solution for 1.5 h with heating maintained until close to complete solution evaporation. The prepared AuNP/BC substrates were stored in deionized (DI) water before use.

Sampling of neonicotinoids onto AuNP/BC substrates for SERS analysis

The SERS spectra of imidacloprid and clothianidin were acquired using the AuNP/BC platform. In this procedure, a single piece of AuNP/BC hydrogel was immersed into a 10 mL analyte solution, with concentrations of 0, 0.05, 0.1, 0.2, 0.5, 1, 2.5, 5, 7.5 and 10 μM. Before introducing the AuNP/BC hydrogel, the solution's pH was adjusted to 2.0 to optimize the affinity between the analytes and the AuNP/BC substrate (Fig. S1). Following the addition of AuNP/BC hydrogel, the container was left at room temperature for 24 h to allow complete adsorption of the analytes onto the SERS substrate. After the incubation, the AuNP/BC hydrogel was retrieved for Raman spectroscopic analysis when it was still wet but without visible water on the surface. Each analyte underwent 6 to 8 replicate tests to ensure accuracy and minimize errors. For each test, an average spectrum was obtained from a 10×10 Raman map across one AuNP/BC substrate. The average spectra were used to calculate the error bars for the 6-8 replicate samples.

Monitoring neonicotinoid adsorption onto AuNP/BC

Prior to adding AuNP/BC into the analyte solutions, 1 mL samples of solutions were collected and analysed using HPLC to establish the initial analyte concentrations (C_i). After the addition of AuNP/BC and a 24-h incubation period, 1 mL samples of solutions were collected again and tested by HPLC to determine the final analyte concentrations (C_f). The differential concentration (ΔC, where $\Delta C = C_i - C_f$) reflected the reduction in neonicotinoid concentrations in the solutions, indicating the quantity of IMD or CLO molecules adsorbed onto the AuNP/BC. The experimental procedure is illustrated in **Fig. 1**. The two most widely used adsorption isotherms – Freundlich

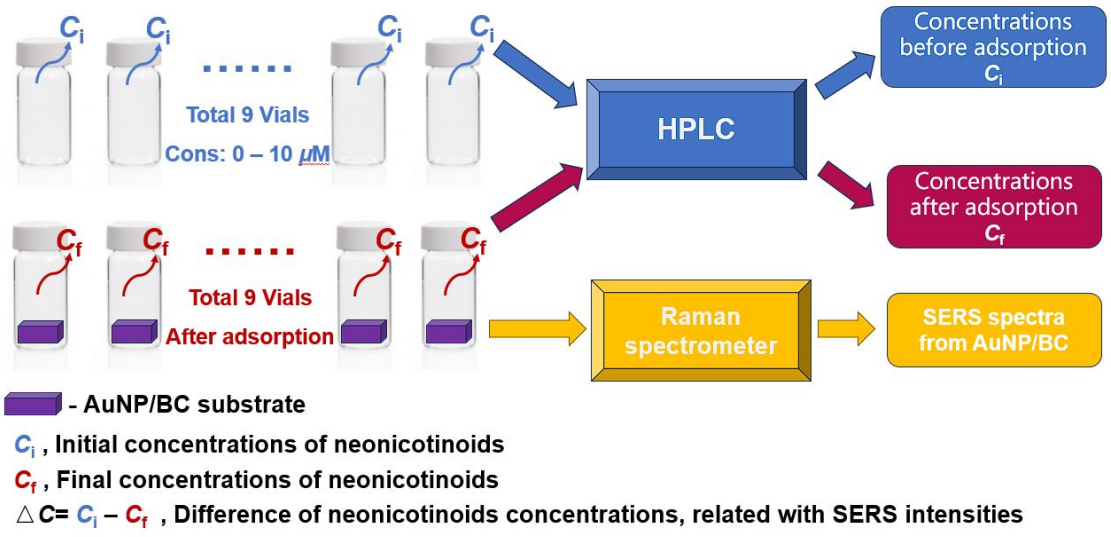

Figure 1. Schematic of the experimental procedure. The initial (C_i) and final concentrations (C_f) of neonicotinoids in aqueous phases were determined by HPLC, with added (nominal) concentrations ranging from 0 to 10 μM. The differential concentrations denoted as ΔC reflect the amount of neonicotinoids adsorbed onto the AuNP/BC substrates. SERS spectra of neonicotinoids were collected from the AuNP/BC substrates using a confocal Raman spectrometer. Our hypothesis posits a quantitative correlation between the hot spot-normalized SERS intensities of neonicotinoids with C_f, and ΔC, driven by adsorption thermodynamics.

and Langmuir models, are employed for adsorption data interpretation, which typically indicate multilayer and monolayer adsorption, respectively. To validate the relationship between SERS intensities and the quantity of molecules adsorbed on substrate surfaces, SERS spectra for IMD were collected from the AuNP/BC substrates after being incubated in IMD solutions of a fixed concentration (0.5 μM) while varying the solution volume between 10 to 100 mL.

Instrumentation

Raman spectra were collected using a confocal Raman spectrometer (Horiba LabRAM HR Evolution). A 10× objective was used to scan a large area and to minimize the impact of SERS substrate heterogeneity. The laser wavelength was set at 785 nm, with an integration time of 1 s and an accumulation of 2 scans. The optical grating was configured at 300 gr/mm. For each AuNP/BC hydrogel, a 10×10 Raman map covering a 100×100 μm^2 area was acquired. Raman spectra ranging from 30 to 1550 cm^{-1} were collected and averaged for each Raman map. All averaged spectra were normalized to the intensities of the elastic band at 47 cm^{-1} after baseline corrections, a process referred to as hot spot normalization,[19-21] to account for the uneven distribution of SERS hot spots across the substrates. Neonicotinoid concentrations in aqueous phases were measured using HPLC (Agilent 1260 Infinity LC System), with specific parameters provided in the Supporting Information (Table S1).

3. Results and discussion

SERS analysis of neonicotinoids

For the analysis of CLO, SERS spectra were acquired from the AuNP/BC substrates incubated in CLO solutions (0 – 10 μM) for 24 h. The Raman bands at 660, 780, 861, 935, and 1067 cm^{-1} were highlighted for CLO identification (Fig. S2). Specifically, the Raman bands at 660 and 861 cm^{-1} were linked to the C-H out-of-plane wagging modes while the band at 780 cm^{-1} was attributed to the N-O out-of-plane wagging modes.[22] The Raman bands at 935 and 1067 cm^{-1} were associated with the C-N stretching modes.[22] Similarly, SERS spectra of IMD were obtained from the AuNP/BC substrates after being incubated in IMD solutions (0 – 10 μM) for 24 h. The Raman bands at 826, 850, 1108, and 1458 cm^{-1} bands were identified as significant features of IMD (Fig. S3). The Raman bands at 826 and 850 cm^{-1} were associated with C-C-C in-plane bending and the torsion of H-C=C-H. The Raman band at 1108 cm^{-1} was indicative of in-phase symmetric stretching of the chloropyridine ring.[23] For CLO and IMD quantification, the intensities of their Raman bands at 660 and 1108 cm^{-1} were normalized using the intensities of the elastic band at 47 cm^{-1} (I_{660}/I_{47} and I_{1108}/I_{47}). This normalization approach effectively mitigated the heterogeneity arising from the uneven SERS hot spot distribution across the AuNP/BC substrate.[19, 20]

Relationship between CLO adsorption and its SERS intensity

To explore the adsorption of CLO onto the AuNP/BC substrates, we initially examined the relationship between the adsorbed amount of CLO (represented by the differential concentrations, ΔC) and its final concentrations in the aqueous phase (Fig. 2a). This relationship can be described using the Freundlich adsorption isotherm (detailed fitting parameters are provided in Table S2), reflecting the heterogeneous sites on the AuNP/BC substrate for CLO adsorption.[24] When only BC was used as the adsorbent, the adsorption capacity for CLO decreased significantly (Fig. 2a). For example, 1.9% of CLO was adsorbed onto BC at an initial concentration of 10 μM while 15% of CLO was adsorbed onto AuNP/BC at the same initial concentration. This highlights the dominant role of AuNPs for CLO adsorption. In addition to the role for CLO enrichment, AuNPs within the AuNP/BC hydrogels also provide numerous intensive SERS hot spots for CLO detection.

For the quantitative analysis of CLO via SERS, hot spot-

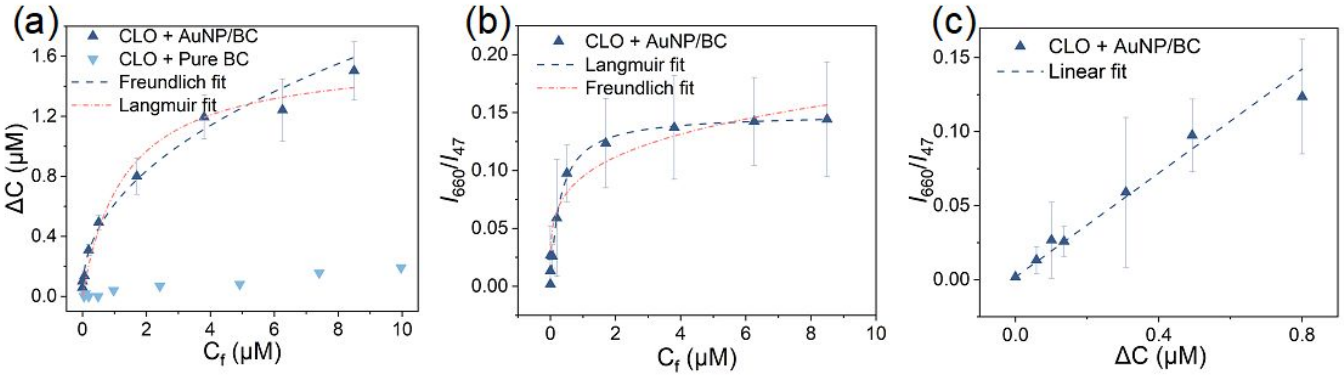

Figure 2. (a) Relationship between the final concentration of CLO (C_f) and its differential concentration before and after adsorption (ΔC). The blue dash and red dash-point-dash lines depict the fitting results of the Freundlich and Langmuir adsorption isotherms for our experimental data, respectively**.** (b) Variation of the normalized SERS intensity of CLO as a function of its final solution concentration, C_f. The blue dash and red dash-point-dash lines depict the fitting results of the Langmuir and Freundlich adsorption isotherms for our experimental data, respectively**.** (c) Variation of the normalized SERS intensity of CLO as a function of its differential concentration, ΔC.

normalized SERS intensity of CLO (I_{660}/I_{47}) was plotted as a function of the initial, final, and differential concentrations in the aqueous phase (C_i, C_f, and ΔC, respectively) as shown in Fig. S4a, Fig. 2b, and Fig. 2c. As reported in our previous study, the

hot spot-normalized SERS intensity showed a linear correlation with the quantity of analyte molecules present on each AuNP.[19-21] The relationship between C_f and the normalized SERS intensity closely aligned with the Langmuir adsorption isotherm (Fig. 2b), indicating that CLO molecules uniformly form a monolayer across the available adsorption sites on AuNP surfaces. This observation significantly contrasts with the scenario depicted in Fig. 2a, where CLO molecules appeared to adsorb on heterogeneous sites or form multilayers on AuNP surfaces. The discrepancy between these findings can be attributed to the distinct measurement methodologies employed. HPLC quantifies the total CLO adsorbed on AuNP surfaces, while SERS specifically targets the monolayer of CLO molecules directly in contact with the AuNP surfaces, a consequence of SERS being a near-field effect. Given the exponential decrease in SERS intensity with increasing distance from the AuNP surfaces, CLO molecules in subsequent layers have a negligible impact on the overall SERS signal.[25]

The correlation between the initial concentration (C_i) and the normalized SERS intensity also fitted well in the Langmuir adsorption isotherm (Fig. S4a). This observation aligns with previously studies in the literature, such as one investigation demonstrating that the adsorption of carbendazim on colloidal silver nanoparticles conforms to the Langmuir model.[26] However, the application of the Langmuir isotherm to elucidate the relationship between C_i and SERS intensity is difficult at the thermodynamic equilibrium of adsorption, where the analyte concentrations in the aqueous phase may change after adsorption. In the Langmuir adsorption isotherm, the fitting parameter "a" represents the maximum normalized SERS intensities, and the parameter "b" reflects the adsorption constant that indicates the affinity of neonicotinoids for AuNP surfaces (Tables S3&4). In our study, Langmuir fitting applied to C_i versus SERS intensity data resulted in an affinity constant approximately half that obtained from fitting the final concentration (C_f) versus SERS intensity data (Tables S3&4). This discrepancy could lead to an underestimation of the detection limit of SERS for analyzing CLO.

In prior research, another common approach for SERS quantification was to plot the SERS intensity against the logarithmic concentrations of analytes,[18] which typically demonstrated a linear relationship. Consistent with these observations, the normalized SERS intensity of CLO in our study also exhibited good linearity with its logarithmic concentration (Fig. S4b). However, this approach does not rest on a solid theoretical foundation and, consequently, falls short of providing a reliable means for predicting SERS performance in analyte quantification. Theoretically, it is anticipated that the normalized SERS intensity is expected to follow a linear trend with the amount of CLO adsorbed onto AuNP substrate ($\triangle C$) rather than with the logarithmic value of its initial concentration in the aqueous phase. Our findings revealed a strong linear correlation between $\triangle C$ and the SERS intensity ($R^2 = 0.99$) for an initial CLO concentration up to 2.5 μM (Fig. 2c), thus validating our hypothesis. Beyond this concentration threshold, however, the relationship deviates from linearity (Fig. S5a). This deviation occurs because the SERS hot spots became saturated with CLO molecules, and subsequent adsorption occurs at less optimal sites.

Validation of our findings using another neonicotinoid

To extend our investigation beyond CLO, we explored IMD, another widely utilized neonicotinoid, to assess how its adsorption onto AuNPs affects the hot spot-normalized SERS intensity. The adsorption of IMD onto bare BC was significantly lower compared with that onto the AuNP/BC composite, further highlighting the dominating role of AuNPs in the adsorption process (Fig. 3a). The relationship between the quantity of IMD adsorbed onto the AuNP/BC substrate ($\triangle C$) and the equilibrium IMD concentration in the solution (C_f) was precisely modelled by a Freundlich adsorption isotherm (R^2 = 0.99, Fig. 3a). This finding aligns with our observations for CLO,

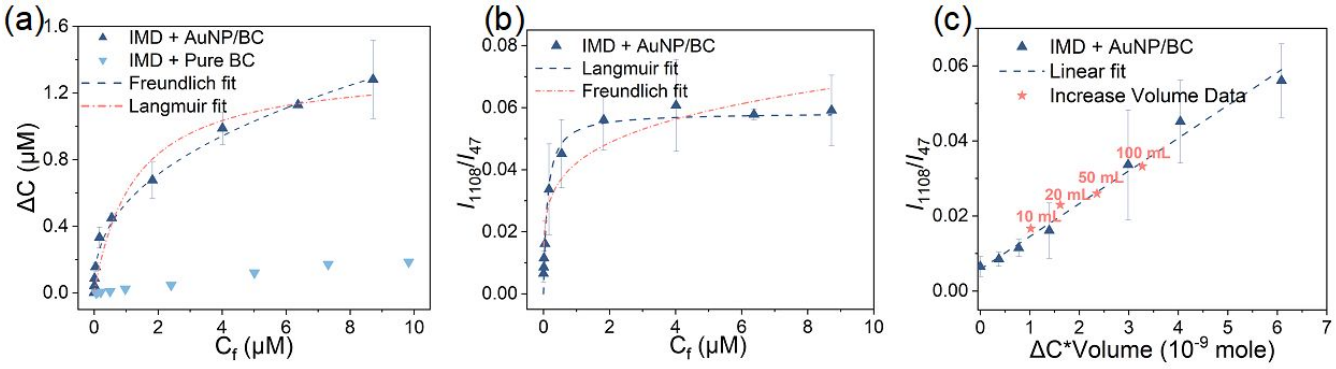

Figure 3. (a) Relationship between the final concentration of IMD (C_f) and its differential concentration before and after adsorption (ΔC). The blue dash and red dash-point-dash lines depict the fitting results of the Freundlich and Langmuir adsorption isotherms for our experimental data, respectively. (b) Variation of the normalized SERS intensity of IMD as a function of its final solution concentration, C_f. The blue dash and red dash-point-dash lines depict the fitting results of the Langmuir and Freundlich adsorption isotherms for our experimental data, respectively**.** (c) Variation of the normalized SERS intensity of IMD as a function of the number of molecules adsorbed on the AuNP/BC substrate, $\triangle C$*Volume. Red stars represent the data points collected at the same IMD concentration of 0.5 μM, with a varying solution volume from 10 to 100 mL. The $\triangle C$*Volume values were calculated using solution volumes of 9, 19, 49, and 99 mL for the initial solution volumes of 10, 20, 50, and 100 mL, respectively.

suggesting that IMD molecules also bind to sites of varying affinities or form multilayers on the AuNP/BC substrate.

The relationship between the final concentrations of IMD in the solution and the normalized SERS intensities also fit well using a Langmuir adsorption isotherm model (Fig. 3b). This suggests that only the IMD molecules adsorbed onto the SERS hot spots across the AuNP/BC hydrogel contributed significantly to the SERS intensities, which is consistent with our observations for CLO (Fig. 2b). Similarly, the correlation of the initial concentration (C_i) and logarithmic initial concentration ($\log C_i$) with the normalized SERS intensity of IMD can be adequately described by a Langmuir and linear model, respectively (Fig. S6). However, as mentioned earlier, these empirical observations lack the capacity for predicting the quantitative performance of SERS for analyzing neonicotinoids. The adsorption constant derived from the Langmuir model fitting of the C_i versus SERS intensity data was approximately 4× lower than that derived from the Langmuir model fitting of the C_f versus SERS intensity data (Tables S7&8). However, a linear regression can precisely describe the relationship between $\triangle C$ and the normalized SERS intensity as the initial IMD concentration was lower than 2.5 μM (Fig. 3c and Fig. S5b). As the initial concentration was higher than 2.5 μM, the relationship deviated from the linear line since the SERS hot spots had been saturated (Fig. S5b).

Implications on SERS quantification

Previous approaches to developing SERS methodologies for detecting trace environmental pollutants typically relied on creating a calibration curve that correlates SERS intensities with either the initial concentrations (C_i) or the logarithm of initial concentrations ($\log C_i$) of contaminants in a solution. This approach often neglects the adsorption dynamics of pollutants from the aqueous phase to the PNP surfaces, potentially leading to an underestimation of the limit of detection (LOD) due to the concentration decrease post-adsorption. Our research has empirically confirmed a linear correlation between SERS intensities and the change in concentration ($\triangle C$), which represents the amount of pollutants adsorbed onto the AuNP/BC substrate. This correlation allows for more accurate determination of the dynamic range and LOD for quantifying water pollutants in subsequent research.

To further support our hypothesis, we maintained the initial concentration of IMD solutions at 0.5 μM and altered the solution volume from 10 to 100 mL to augment the number of IMD molecules adsorbed on the AuNP surfaces. We anticipated a linear relationship between the SERS intensities and the quantity of adsorbed molecules on the substrate. Figure 3c illustrates this, with the x-axis denoting the adsorbed molecules on the substrate ($\triangle C$*Volume) in units of 10^{-9} moles. With increasing solution volume, the data points (indicated by red stars) for volumes of 10, 20, 50, and 100 mL closely followed the linear prediction model established earlier in our research. This finding emphasizes the necessity of accounting for adsorption effects on the substrate surface and reveals that initial concentration (C_i) alone is insufficient for accurate analysis. Our results confirm that the number of molecules adsorbed on the substrate surface is the pivotal factor affecting SERS signals.

This validation, obtained by varying the solution volume while keeping the concentration constant, implies that larger volumes can enhance SERS intensities by reducing the difference in solution concentrations before and after adsorption. Considering the vast volume of natural or engineered water bodies, using a flow-through device that enables a substantial volume of water to interact with the AuNP/BC surface may produce consistent SERS spectra suitable for quantification. Furthermore, establishing a correlation between the flow-through volume and SERS signals on the substrate, and factoring in neonicotinoid adsorption, paves the way for applying this technique in field research.

Summary and conclusions

This research investigates the adsorption of neonicotinoids on SERS substrates and their resultant SERS intensities by correlating C_i, C_f, and $\triangle C$ with the SERS intensities. Our findings underscore that the crucial link between SERS intensities and neonicotinoid concentrations lies in their adsorption thermodynamics on AuNP surfaces. The relationship between SERS intensities and C_f aligns with the Langmuir adsorption isotherm, reflecting saturation of SERS hot spots at elevated neonicotinoid concentrations, despite the continuous increase in the amount adsorbed on the substrates. Prior to reaching this saturation, the adsorption of IMD and CLO molecules on AuNP surfaces demonstrated a linear correlation with SERS intensities. This research provides a new perspective on quantitative SERS analysis, highlighting the significant role of neonicotinoid adsorption. More efforts should be directed towards understanding the adsorption dynamics of analytes to achieve precise quantification.

Author contributions

Conceptualization (Liu and Wei), Formal analysis (Liu and Wei), Methodology (Liu, Lazarcik, and Wei), Writing – original draft (Liu), Writing – review & editing (Liu, Lazarcik and Wei).

Conflicts of interest

There are no conflicts of interest to declare.

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