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Supramolecular Low-Molecular-Weight Hydrogelator Stabilization of SERS-Active Aggregated Nanoparticles for Solution and Gas Sensing

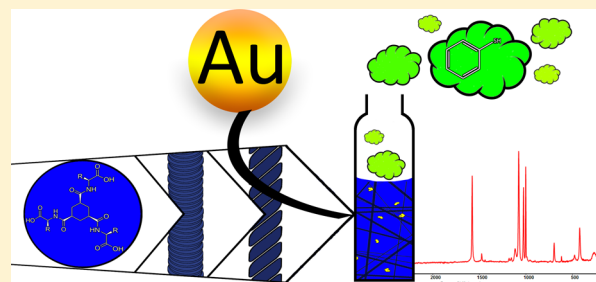
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Supporting Information

ABSTRACT: The potential of surface-enhanced Raman scattering (SERS) spectroscopy in both laboratory and field analyses depends on the reliable formation of so-called SERS hot spots, such as those formed during gold or silver nanoparticle aggregation. Unfortunately such aggregates are not stable in solution because they typically grow until they precipitate. Here we describe the use of low-molecular-weight hydrogels formed through pH-triggered self-assembly that occurs at a rate that well matches the rates of aggregation of Au or Ag colloids, allowing them to be trapped at the SERS-active point in the aggregation process. We show that the colloid-containing gels give SERS signals similar to the parent colloid but are stable over several months. Moreover, lyophilized gels can be stored as dry powders for subsequent use in the analyses of gases and dissolved analytes by contact with either solutions or vapors. The present system shows how the combination of pH-switchable low-molecular-weight gelators and pH-induced colloid aggregation can be combined to make a highly stable, low-cost SERS platform for the detection of volatile organic compounds and the microvolume analysis of solutions.



INTRODUCTION

Surface-enhanced Raman scattering (SERS) is characterized by increased Raman scattering by molecules situated near to or on rough metal surfaces. Numerous materials have now been shown to give SERS enhancement, including sophisticated systems which, for example, attempt to create uniform plasmonic enhancements over large areas by controlling the nanostructure.^{1–6} However, for many practical applications aggregated metal nanoparticles continue to be of interest because of both their low cost and simplicity and the large plasmonic enhancements they provide.^{7,8} Indeed, the first single-molecule SERS measurements used aggregated particles.⁹ It is now widely accepted that particle aggregation is necessary to create the so-called hot spots of high local field intensities that are situated at the points where particles almost touch.^{8,9} Unfortunately, it is difficult to create stable aggregates of a given size, and most experiments on aggregated colloids are therefore carried out in the time window where sufficient aggregation has occurred to give SERS enhancement but before the aggregates grow so large that they precipitate out of the suspension. This aspect has led to considerable work over the past decade aimed at controlling and stabilizing aggregates by trapping them within hydrogel hosts that act as particle scaffolds. The primary requirement is to trap the aggregates while still allowing access by the target molecules that must reach the surface to be

enhanced. Many groups have focused on stabilizing aggregated particles in aqueous solutions by introducing (natural and synthetic) polymer-based hydrogels.^{10–16} The stabilization of particles held within low-molecular-weight hydrogelators (LMWG) has been achieved through the use of gelators that interact strongly with aggregates; however, this approach resulted in an enhancement of the Raman scattering of the gelator rather than the detection of added molecular targets.^{17,18}

In this article, we demonstrate the use of a simple, biocompatible, pH-switchable hydrogel based on the self-assembly of a low-molecular-weight hydrogelator composed of a cyclohexane core decorated with three amino acid chains (Figure 1) as a new scaffold for colloidal SERS. Previous studies have shown that these gels are quite versatile, are tolerant to high concentrations of salts, are thermostable, nontoxic and environmentally benign.^{19–21} In principle, these LMWGs should be ideal scaffold materials since the gelation process can be switched, allowing the particle aggregation and trapping

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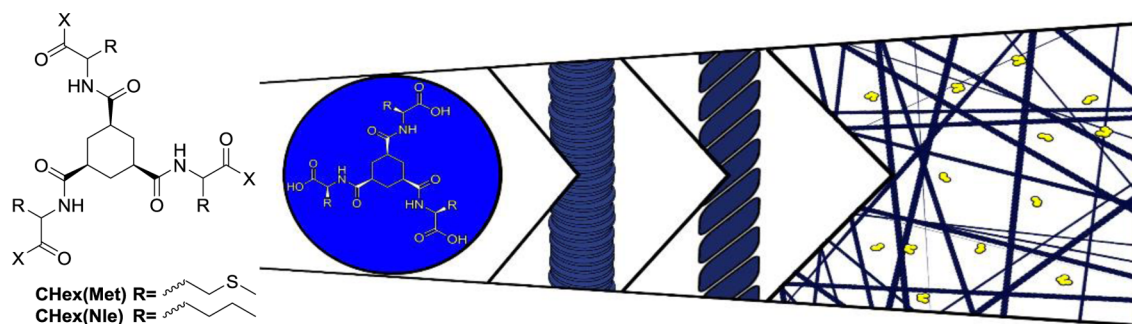


Figure 1. Structure of low-molecular-weight organogelators CHex(Met) and CHex(NLe) and a representation of trapped aggregated nanoparticles.

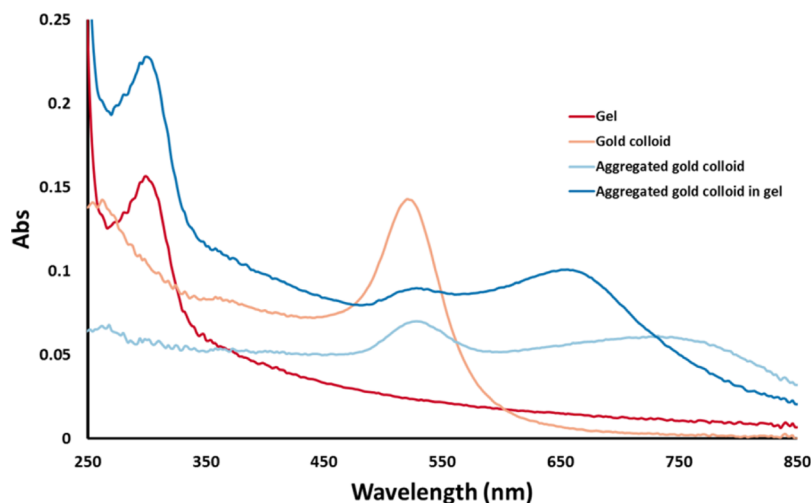


Figure 2. UV-vis absorption spectra of (NaOH/HNO₃) aggregated colloid: (red) CHex(Met) (2 mg cm⁻³) hydrogel alone, (orange) gold colloid prior to precipitation, (light blue) colloid 10 s after the addition of HNO₃ (to pH 3), and (dark blue) colloid held in hydrogel several minutes after the addition of HNO₃. Spectra were recorded in 1 mm path length cuvettes positioned directly in front of the entrance to an integrating sphere to gather scattered as well as transmitted light. The NP concentration is estimated to be 1.66 × 10¹² nonaggregated particles per 1 mL of gel.

processes to be synchronized and controlled. Moreover, the gelators are expected to have relatively weak interactions with Ag or Au surfaces, so they should also allow analytes to access the particles. The model compounds used in this paper are thiophenol, chosen because it is a well-known SERS test material, which will allow ready comparison with other enhancing materials and aminothiophenol, because it is a solid with a low vapor pressure, which is useful for situations where evaporation/head space analysis is concerned. Aminothiophenol is used as a corresponding nonvolatile analog of thiophenol.

EXPERIMENTAL SECTION

Compounds CHex(Met) and CHex(Nle) were available from earlier studies.¹⁹ Silver and gold colloids were prepared using the method described by Grabar et al., with a full description and characterization provided in the SI.²² All preparations were performed using doubly distilled water. All reagents were purchased from Sigma-Aldrich and used without further purification. All measurements were performed in duplicate or triplicate.

For the preparation of hydrogels, 800 μL of a Ag- or Au-colloid-containing solution was added to 100 μL of CHex(Met) (20 mg mL⁻¹) in 1 M NaOH(aq). The addition of 100 μL of 1 N acid(aq) (HNO₃, H₂SO₄, H₃PO₄, or HCl) to the mixture with gentle agitation resulted in a change in color (from yellow to gray in the case of the Ag colloid and red to blue in the case of the Au colloid) concomitant with the formation of a hydrogel. For experiments in microtiter (96 well) plates, lower volumes were used with the same volume ratios. During

time-dependent measurements the gels were held in closed vials at room temperature to prevent solvent evaporation. Lyophilization was carried out using a Christ Alpha 2-4 LDPlus. An ingress of thiophenol into lyophilized hydrogel-stabilized colloid was carried out by placing the powder in a sealed box together with a tray of thiophenol for 1 h, followed by removal and storage in air for 10 min before the measurement of its Raman spectrum at 632.8 nm.

UV-vis absorption spectra were recorded on a JASCO 570 UV-vis-NIR absorption spectrometer equipped with an integrating sphere. Unless stated otherwise, Raman spectra were recorded at 785 nm, including mapped data, using a PerkinElmer Raman station. Raman spectra were also recorded using an Olympus BX51 M upright microscope with excitation at 632.8 nm (Thorlabs HNL 120-1 HeNe laser) and 10 mW at the sample, with appropriate laser line clean-up filters from Semrock. Excitation was delivered using a dichroic mirror (Semrock) and light was collected via a round to line multicore fiber (which acted as a slit) and delivered to a Shamrock 163 spectrograph and dispersed with an SRT-SHT-9003 grating onto a iDus-416 CCD detector (Andor Technology). Calibration was performed using the spectrum of polystyrene. Dropping ball measurements were carried out using a Thermo Scientific HAAKE DC30 circulator filled with paraffin oil connected to a six-sample heating block. The temperature of the heating block was recorded using a Amarell Electronic digital thermometer, and the ball was followed using a Logitech C270-HD webcam. TEM images were recorded on a Phillips CM10 with a LaB₆ emitter. Rheology was carried out using an Anton Paar parallel plate rheometer. Dropping ball and rheological measurements were carried out as described earlier.¹⁹

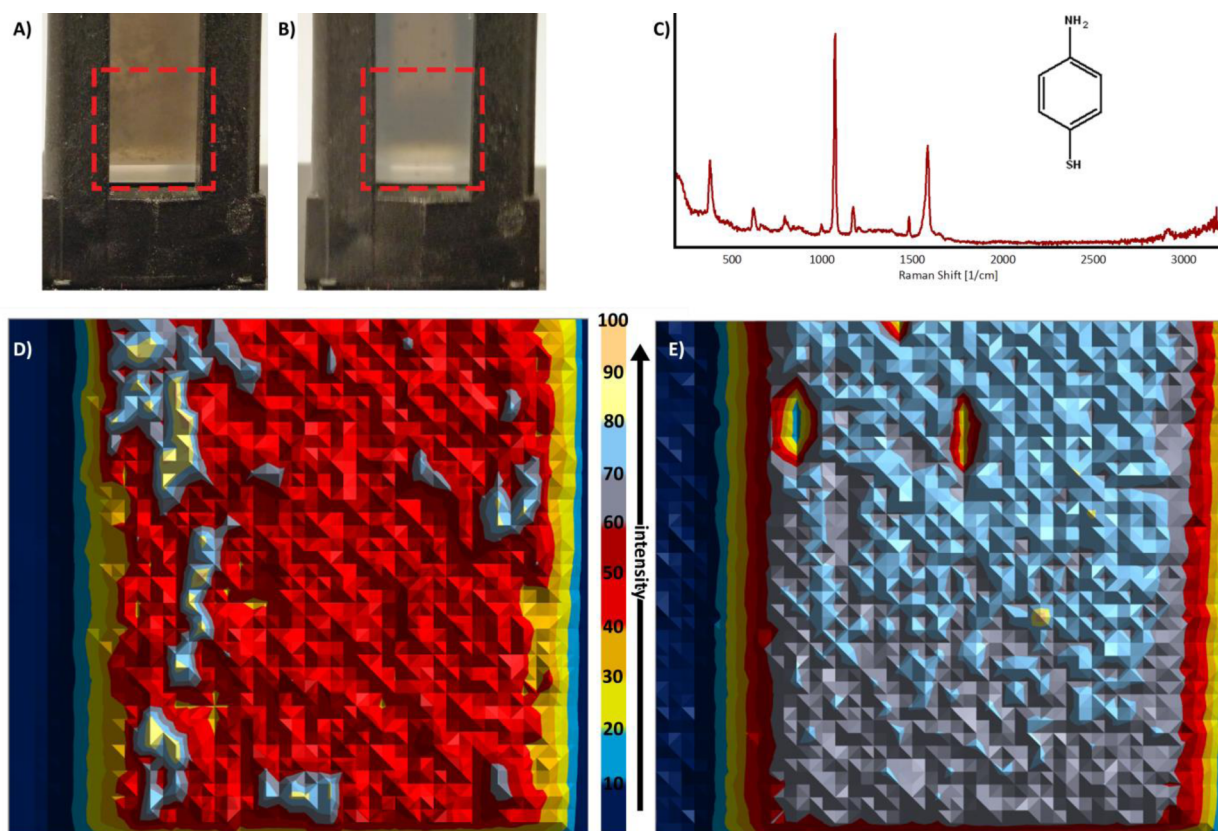


Figure 3. Hydrogel-containing aggregated (A) Ag and (B) Au colloids; the areas imaged by Raman spectroscopy are indicated by a red square. (C) SERS spectrum of aminothiophenol at 785 nm. Intensity maps (at 1550 cm^{-1}) for (D) Ag- and (E) Au-colloid-containing hydrogels.

RESULTS AND DISCUSSION

In the present study, thiophenol and aminothiophenol were selected as test analytes because of their chemical (both are aurophilic) and spectroscopic similarity and their volatile and nonvolatile character, respectively. The Raman spectra of both compounds show a series of sharp, characteristic bands (Figures S1 and S2) that are readily distinguishable from the Raman bands of other components, such as the LMWGs, citrate, and inorganic anions employed in the present study.

The aggregation of Ag and Au colloids upon addition of inorganic acids resulted in a transient increase in SERS activity for aryl-thiols, which decreased concomitantly with the subsequent precipitation of the colloid as expected. Under the present conditions, concentrations of ca. $10\ \mu\text{M}$ gave strong signals for both thiophenol and aminothiophenol (Figures S4 and S5), and hence this was used as the standard concentration throughout.

The addition of either colloid to solutions of either low-molecular-weight gelator at pH 10 did not result in significant changes to their color (visible absorption), indicating that aggregation was not induced by the LMWGs. The addition of sufficient inorganic acid to the mixtures of colloid and LWMG to decrease the pH to 3 resulted in the aggregation of the colloid (manifested in a change in color and an increase in SERS scattering) concomitant with a dramatic increase in viscosity, indicating the formation of a hydrogel. The Raman spectra of thiophenols and aminothiophenols obtained in the presence of the gelator are identical to those recorded with simple Ag and Au colloids aggregated by the addition of acid to reduce the pH to 3 (Figures S6 and S6). However, whereas the

enhancement is lost as the particles settle in the absence of the LMWGs, the SERS spectrum obtained with the hydrogel present persists unchanged for at least several days.

Consistent with the SERS measurements, the absorption spectra of the Ag and Au colloids undergo a substantial red shift and broadening upon a drop in pH to 3 (Figure 2 and Figure S8). The shifts are characteristic of the changes in surface plasmon resonance energy upon aggregation and continue over time, ultimately leading to the precipitation of the colloid. The opacity of the hydrogels due to scattering necessitated the use of an integrating sphere to record absorption spectra; however, similar initial changes to the visible spectrum upon aggregation (and gelation) were observed. Although the spectra of the silver colloid in the presence and absence of gelator are both broad, the spectra of the Au colloid shows a reduced extent of aggregation (less red shift in the surface plasmon resonance) that stops changing once the solution had undergone gelation, confirming that gelation inhibits further aggregation. The spectra of both Ag and Au colloids when trapped in the hydrogels did not undergo further changes over several hours, whereas the spectra in the absence of the hydrogels showed that the colloid underwent relatively rapid precipitation.

As reported earlier,¹⁹ the addition of salts to solutions containing the hydrogelators results in a substantial increase in the thermal stability of the hydrogels. The presence of the gold or silver colloids affected neither the melting temperature nor the rheological properties (G' and G'') of the gels significantly (Figure S9), indicating a relatively weak interaction between the gel fibers and the colloidal particles. However, it should be noted that the concentration of gold nanoparticles is low (0.007 wt %), and hence any interaction between the gel fibers and

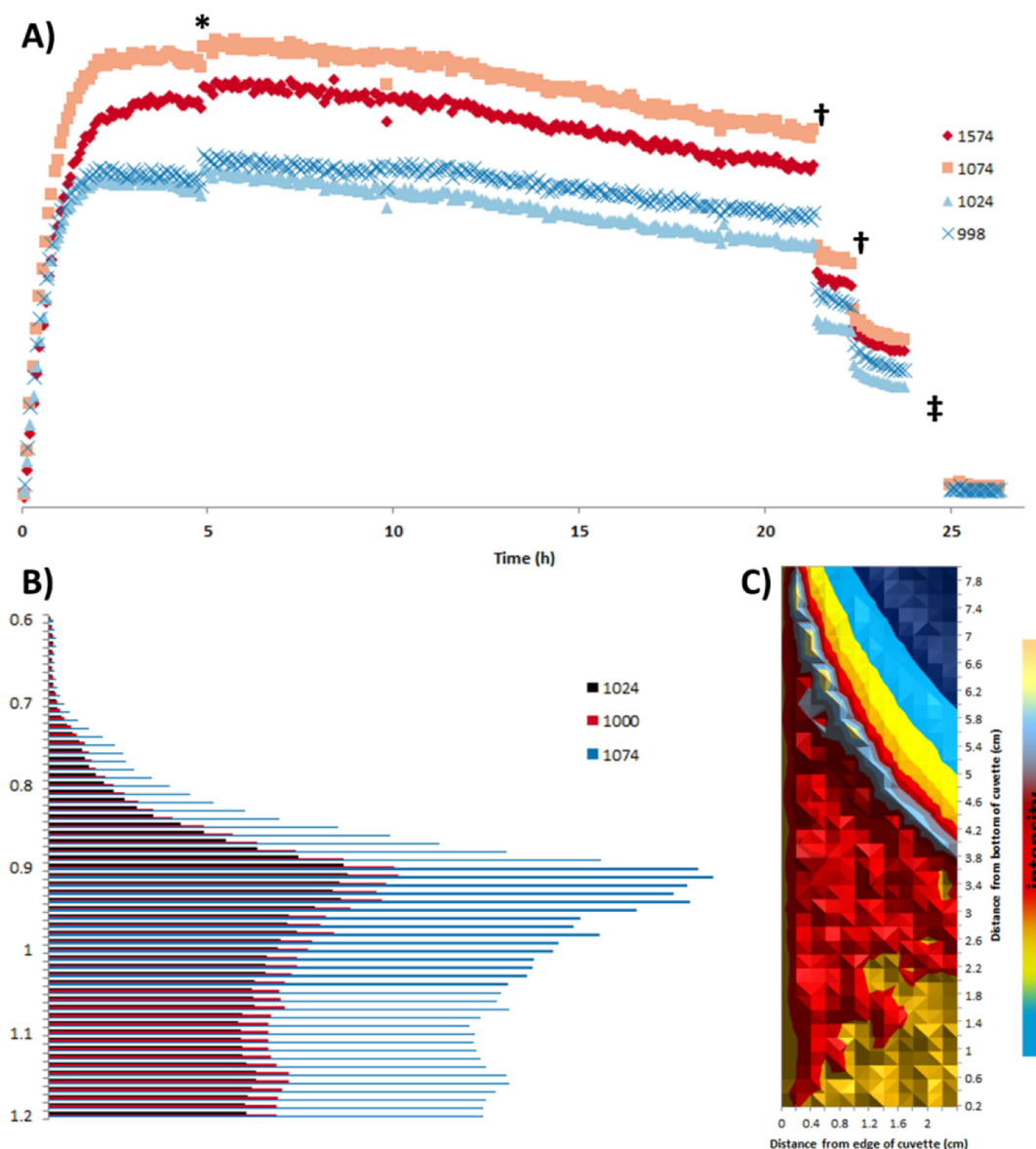


Figure 4. (A) Intensity of four Raman bands of thiophenol over time in a cuvette with 1 mL of CHex(Met) hydrogel containing an aggregated gold colloid with a droplet of thiophenol placed in the headspace above the gel. After 5 h, the cap and thiophenol droplet were removed, and after 21 and 22 h (†), the cuvette was placed open in a fume hood for a few minutes and after 23 h it was left to stand in a fume hood for 1 h (‡). (B) Signal intensity as a function of depth into the hydrogel before removal of the cap. (C) Raman intensity at 1550 cm^{-1} within the hydrogel. *Changes in intensity are due to the repositioning cuvette.

gold nanoparticles is unlikely to impact the gel macroscopic properties substantially. The thioether unit of the CHex(Met) gelator is unlikely to interact significantly with the gold nanoparticles, and indeed other related gelator structures such as CHex(NLe) gels show the same properties in terms of the SERS spectra obtained with silver and gold colloids and stability (Figures S9 and S10).

Distribution of Aggregated Colloids in Hydrogel Matrixes. A key challenge in the application of SERS spectroscopy lies in quantitative analysis. In solution, the time-averaged spectrum is essentially constant as a result of Brownian motion. In the gel state, the partially aggregated gold colloid is trapped spatially within the hydrogel fiber matrix, and the strength of the SERS spectrum is dependent on the number of aggregated particles within the confocal volume. Hence, the spatial uniformity, which is dependent on the rate of gel fiber formation relative to the rate of colloid aggregation following

the pH jump, will determine the reproducibility of the SERS signal intensity. The mapping of Ag and Au colloids trapped within a hydrogel containing aminothiophenol ($10\ \mu\text{M}$) in a 1 cm cuvette with 0.1 mm steps (over an area of $8 \times 9\ \text{mm}^2$) was carried out, and the absolute intensity of the band at $1550\ \text{cm}^{-1}$ was used to generate heat plots (maps using other bands are essentially identical). The heat plot obtained with Ag colloids indicated that the spatial distribution was not uniform, especially in comparison to the heat plot obtained with the Au colloid, which indicates that the aggregation of the Au colloid is slower and therefore suspended at an earlier stage than for the Ag colloid. The average intensities are ca. 47% (S.D. 10%) and 69% (S.D. 3.6%) of the maximum intensity for hydrogel-stabilized Ag and Au colloids, respectively. These data are also consistent with the absorption spectra of the colloids (vide supra). The difference in uniformity of the hydrogel-stabilized Ag and Au nanoparticles in the present case

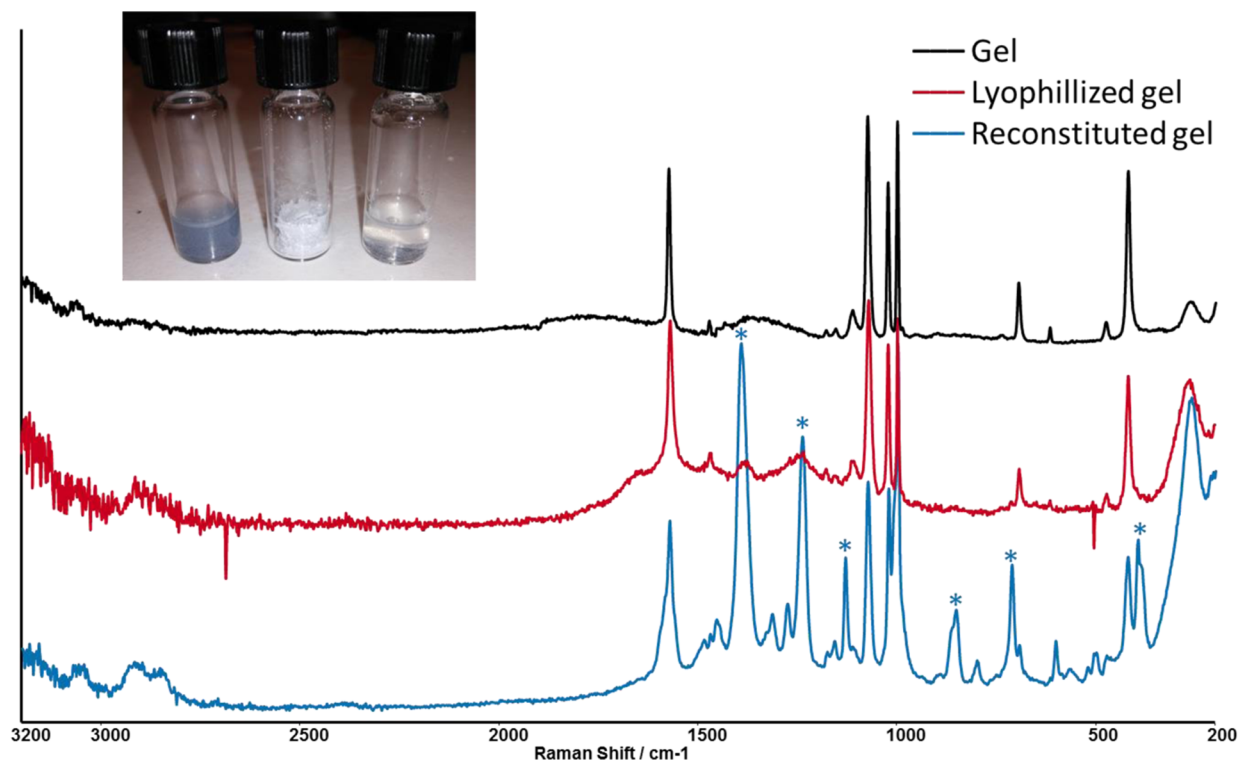


Figure 5. Raman spectrum of (ca. $1 \mu\text{M}$) thiophenol in (black) CHex(Met) hydrogel with the NaNO_3 aggregated gold colloid. (The glass background signal has been removed by scaled subtraction.) (Red) Raman spectrum obtained by the addition of $10 \mu\text{L}$ of aqueous thiophenol ($5 \mu\text{M}$) placed on top of a lyophilized gold colloid containing hydrogel powder and (blue) reconstituted hydrogel with thiophenol (ca. $1 \mu\text{M}$) * SERS bands of citrate. (Spectra are obtained at λ_{exc} 785 nm, with 4×5 , 10, and 10 s acquisitions respectively).

highlights a general challenge in using the absolute intensity in quantitative work. The flexibility of the present system in terms of the acids used for the gel-forming pH jump does offer the prospect of using the inorganic anions as internal reference signals that could correct for changes in focus or laser power, but of course for critical quantitative analysis a SERS-active internal standard is preferable because it could also correct for differences in the number-average of Raman hotspots with the confocal volume.⁵ Furthermore, over long periods of laser excitation, local heating induces movement of the colloidal particles through the gel matrix and hence a minor drift in signal intensity over extended periods of irradiation (vide infra, Figure 4).

Detection of Gases by Hydrogel-Stabilized Colloids through Reversible Gas Uptake and Release. The open hydrogel scaffold provides for a sufficiently rigid matrix to prevent/limit convection and translation movement of the aggregated nanoparticles but simultaneously is a primarily aqueous state that allows for the diffusion of molecules partitioning from the head space. Their stability allows even relatively slow processes such as the diffusion of gas into the matrix to be measured. The spatial distribution of the SERS spectrum obtained from a hydrogel-stabilized gold colloid after saturation of the headspace above the gel with thiophenol gas was determined. The Raman bands of thiophenol increased in intensity steadily and eventually leveled off over a period of 5 h. Measurement of the spatial distribution of the Raman spectrum from 0 to 1 cm depth shows clearly the penetration depth of the thiophenol over this period. As expected for mass transfer by diffusion only, the signal is highest at the surface of the gel in contact with the gas and, after a certain depth, gradually decreases. Release of the gas from the cuvette when opened

occurred slowly when uncapped but held overnight within a closed sampling compartment (ca. 35 L) and more quickly when the cuvette was placed in a flow of air with eventually nearly complete loss of the signal of the analyte.

Long-Term Stability. The stability of gels containing colloids stored in sealed vials at ambient temperatures was apparent from the absence of changes in morphology (e.g., crystallization or the appearance of fluid) over at least a 3 month period. The SERS response to the injection of thiophenol gas into the headspace above the gel was qualitatively similar in all cases (using the strong nitrate band as a pseudointernal reference, Figures S11 and S12). However, for longer-term storage, the lyophilization of the gel was explored as a means of preserving the stabilized aggregates in a dry form, which can be reconstituted before use, mixed directly with analyte solutions, or used as a dry powder for gas analysis.

SERS Activity before and after the Reconstitution of Lyophilized Gels. The hydrogels discussed in the present contribution have previously been shown¹⁹ to be stable upon lyophilization so that subsequent reconstitution of the gel by the addition of pure water followed by a heating/cooling cycle restores the gel's original properties (e.g., rheology, melting point, etc.). However, with the particle containing lyophilized gels, although the gel properties recovered fully, the blue color of the colloid/gel mixture was lost upon heating, presumably as a result of increased aggregation when the gel structure was disrupted at high temperature. The SERS spectra obtained (after the addition of thiophenol through exchange from the head space to the gel) from colloid containing hydrogel reconstituted by heating and cooling showed primarily bands due to SERS enhancement of the Raman scattering of citrate (Figure S14), present as a stabilizer of the gold colloid, in

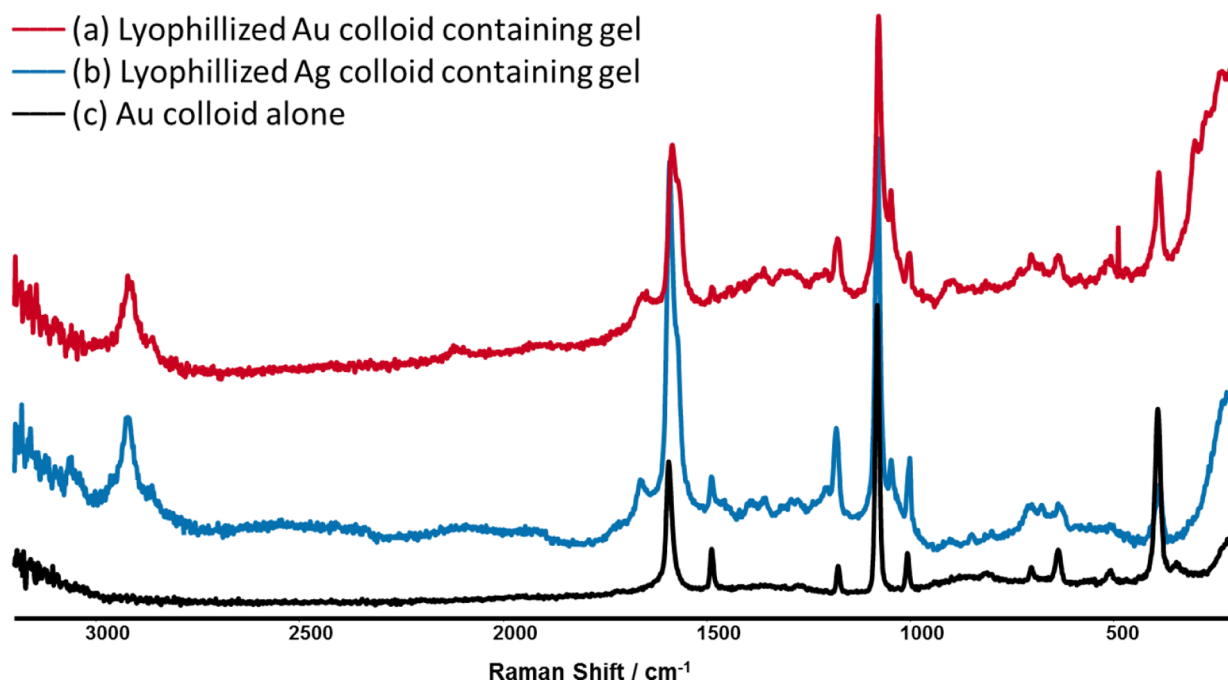


Figure 6. Raman spectra of a 100 μL droplet of water containing (10 μM) aminothiophenol placed on a lyophilized gel containing (a) Au colloid, (b) Ag colloid, and (c) a Raman spectrum of (10 μM) aminothiophenol obtained in an aggregated gold colloid with HNO_3 .

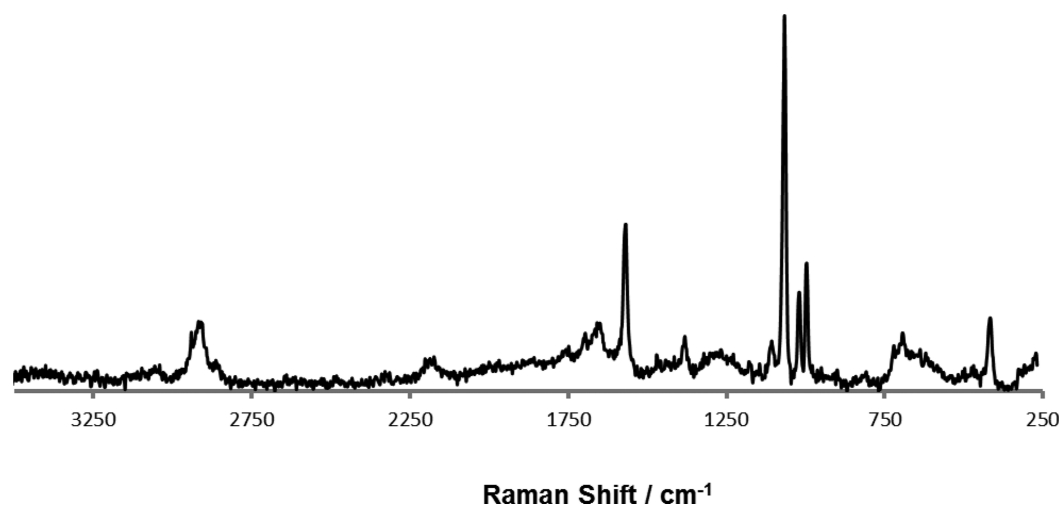


Figure 7. SERS spectrum at 632.8 nm for Au colloid stabilized in a lyophilized CHex(Met) hydrogel that had been exposed to thiophenol vapor.

addition to that of the thiophenol. The pronounced surface enhancement, even after reconstitution by heating/cooling, albeit marginally weaker than for the original gel, together with the change in color indicates that further aggregation of the colloid has occurred but not precipitation. However, the rapid heating–cooling cycle is unlikely to be easily reproducible, from a quantitative perspective, which together with interference from the enhancement of scattering from citrate makes this approach less useful.

More significantly, however, the addition of a drop of water containing the analyte (thiophenol) directly onto the lyophilized (dried) gels resulted in the appearance of a strongly enhanced SERS signal (Figure 5).

Similarly, the spectra obtained from lyophilized hydrogels containing Ag and Au colloids upon addition of 100 μL of aqueous aminothiophenol (10 μM) are similar to those obtained with aggregated Au colloid alone. Furthermore, the

presence of water is not essential for SERS spectra to be obtained from the lyophilized gels, as demonstrated by the intense SERS spectrum obtained from a sample stored in a sealed box in which the headspace was saturated with thiophenol gas and subsequently removed to air for analysis (Figure 7). The ready uptake and retention of thiophenol by the lyophilized hydrogel via the headspace resulting in a substantial SERS enhancement is unexpected but likely reflects the open porous structure of the hydrogel framework facilitating gas ingress. This property is important because it opens the opportunity to use this class of support for long-term gas analysis by SERS because the colloid is locked in its partially aggregated state by the absence of solvent but is still accessible to gaseous as well as liquid analytes

CONCLUSIONS

The organic gelators shown here are excellent as scaffolds for nanoparticle aggregates because the pH switching that induces supramolecular aggregation and thereby gelation also induces particle aggregation concomitantly. The rate of particle aggregation is on a time scale similar to that of gel fiber formation, and hence the colloid is trapped in the aggregated state but precipitation is prevented. The hydrogel scaffolds may interact with the colloid through its carboxylic acid groups in the same manner as citrate stabilizes gold colloids; however, the similar behavior of the methionine and norleucine-based hydrogelators indicates that the sulfur unit in the former is not involved. Importantly, the hydrogel gives a low SERS response, and hence interference with the spectra of analytes is minimized. The stability of the hydrogel colloids to lyophilization and its open structure are important in the analysis of volatile target molecules. For the materials in the hydrogel state, the ability of the target molecules to access the enhancing surface is not unexpected because the aggregates are held within an open hydrogel fiber network (with 0.1 wt % of the structure comprising the gel fibers), and although convection is precluded, diffusion is unaffected. More importantly for practical purposes, the accessibility of the surface is retained even after the gels have been lyophilized and hence have a substantially long lifetime. Rehydration with analyte-containing solution brings the analyte molecules directly into contact with the released particles, allowing SERS detection. Finally, the ability to take up analytes from the headspace, reversibly, in the hydrogel and the detection using a lyophilized powder open up many opportunities for application in long-term real-time air analysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.langmuir.7b01445.

Preparation of gold and silver colloids. TEM images. SERS, Raman, and UV-vis spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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