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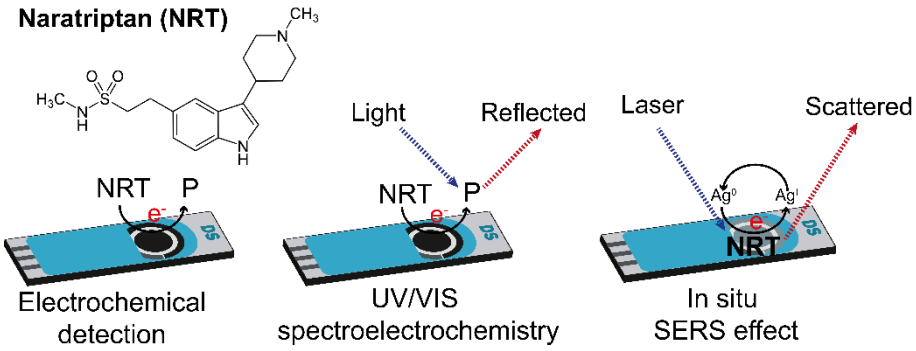

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Evaluation of electrochemical, UV/VIS and Raman spectroelectrochemical detection of Naratriptan with screen-printed electrodes

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Abstract

Naratriptan, active pharmaceutical ingredient with antimigraine activity was electrochemically detected in untreated screen-printed carbon electrodes (SPCEs). Cyclic voltammetry and differential pulse voltammetry were used to carry out quantitative analysis of this molecule (in a Britton-Robinson buffer solution at pH 3.0) through its irreversible oxidation (diffusion controlled) at a potential of +0.75 V (vs. Ag pseudoreference electrode). Naratriptan oxidation product is an indole based dimer with a yellowish colour (maximum absorption at 320 nm) so UV-VIS spectroelectrochemistry technique was used for the very first time as an *in situ* characterization and quantification technique for this molecule. A reflection configuration approach allowed its measurement over the untreated carbon based electrode. Finally, time resolved Raman Spectroelectrochemistry is used as a powerful technique to carry out qualitative and quantitative analysis of Naratriptan. Electrochemically treated silver screen-printed electrodes are shown as easy to use and cost-effective SERS substrates for the analysis of Naratriptan.

Keywords: Naratriptan, screen-printed electrodes, UV-VIS and Raman Spectroelectrochemistry, SERS

1. Introduction

Active pharmaceutical ingredient Naratriptan (N-methyl-3-(1-methyl-4piperidyl)indole-5-ethanesulfonamide) is a selective agonist of serotonin, commonly used for the treatment of migraine headaches causing vasoconstriction[1,2]. Its analytical determination was always related to chromatographic[3,4], mass spectrometry[5,6] or colorimetric[7] techniques, and only a previous work dealing with its electrochemical detection has been already published[8]. A one electron oxidation process has been suggested for this molecule generating a cation radical that later dimerizes through the position number 3 in the indolic ring (Figure 1). This oxidation product is stable enough to be detected optically after the electrochemical reaction and has a yellowish colour in aqueous solution, however to the best of our knowledge the *in situ* UV-VIS spectroscopic study of the electrochemical oxidation of Naratriptan has not been yet performed. Therefore, UV-VIS spectroelectrochemistry has been selected here as an in situ and real-time characterization and quantification technique because a more complete and specific information can be obtained. The miniaturized three electrode cell of screen printed carbon electrodes that only needs a drop of solution inside a reflection cell makes the experimental setup easy and reproducible in comparison with conventional electrodes[9–11]. UV-VIS spectroelectrochemistry is an autovalidated analytical technique and has been already used in combination with screen printed electrodes to follow the electrochemical reduction of graphene oxide[12], for the detection of biological active molecules like dopamine[13], herbicides like glyphosate[14] or hydrogen peroxide[15].

Raman spectroelectrochemistry is usually performed as a characterization technique to identify specific electrochemical oxidation or reduction products due to their characteristic fingerprint spectrum. It has also been well reported the use of electrochemical pretreatments as roughening steps to get SERS effect in the surface of metallic or nanostructured electrode materials[16,17]. However only a couple of works have already been published dealing with screen-printed electrodes and Raman Spectroelectrochemistry for the quantitative analysis of uric acid and melamine[18,19]. Therefore, to the best of our knowledge in this work screen-printed silver electrodes are shown for the very first time as cost-effective SERS substrates for the sensitive and quantitative detection of Naratriptan.

2. Experimental

2.1 Instrumentation

Voltammetric measurements were performed with a portable bipotentiostat/galvanostat μSTAT400 (DropSens, Spain) controlled by DropView 8400 2.2 software. UV-VIS Spectroelectrochemistry was carried out with UV-VIS SPELEC instrument (DropSens, Spain) used in combination with a bifurcated reflection probe, working in a near normal reflection configuration in a reflection cell (DRP-REFLECELL, DropSens, Spain). Raman Spectroelectrochemistry was performed using RAMAN SPELEC instrument (laser 785 nm), a Raman probe and a specific Raman Cell for screen printed electrodes (DropSens, Spain). Both spectroelectrochemical instruments were controlled by DropView SPELEC 2.0 software.

2.2 Reagents and solutions

Naratriptan was purchased from Sigma and stock solutions were prepared in Britton–Robinson solution for voltammetric and UV-VIS spectroelectrochemical assays and in 0.1 M KCl solution for Raman spectroelectrochemistry measurements. Potassium chloride, sodium hydroxide and boric acid were also purchased from Sigma (Spain). Ortho-phosphoric acid (85%), acetic glacial (100%), were provided by Merck. All other chemicals employed were of analytical reagent grade. Ultrapure water obtained with a Millipore Direct-Q^{TM} purification system from Millipore Ibérica S.A. (Spain) was used throughout this work.

2.3 Screen-printed electrodes (SPEs)

The DropSens´ electrodes incorporate a three-electrode cell configuration printed on ceramic substrates (dimensions: 3.4 x 1.0 x 0.05 cm; length x width x height) and were previously described[20]. Carbon working (disk-shaped 4 mm diameter, DRP-110) and silver working electrodes (disk-shaped 1.6 mm diameter, DRP-C013) were used in combination with counter-electrodes made of carbon ink, whereas pseudoreference electrode and electric contacts are made of silver. Voltammetric measurements were performed by placing a 50 µl drop of the corresponding solution to the working area, whereas UV/VIS and Raman spectroelectrochemical measurements were performed using drops of 100 µL and 60 µL, respectively.

2.4 Density functional theory calculations

Nwchem quantum chemistry software[21] was used to estimate the theoretical vibrational frequencies of naratriptan. The calculations were performed using density functional theory (DFT) at the B3LYP theoretical level and the SVP basis set. The effect of the solvent was accounted for using the COSMO solvation model[22]. No

imaginary frequencies were found. The predicted frequencies were multiplied by a scaling factor of 0.987.

3. Results and Discussion

Naratriptan (NRT) shows an irreversible anodic peak at +0.75 V (vs Ag pseudoreference electrode) when it is oxidized by cyclic voltammetry in aqueous solution (0.1 M Britton-Robinson buffer solution, pH = 3.0) in the surface of untreated screen-printed carbon electrodes (Figure 2A, blue color line). Velasco-Aguirre et al. have studied the different voltammetric behaviour at different pH values and concluded that pH 3 leads to a well-resolved and stable analytical signal [8]. By performing the cyclic voltammetry experiments at different scan rates (50-500 mV/s), it was found that the oxidation is a diffusion controlled process with equation: i_p (μA) =1.01 $v^{1/2}$ ($\mu A \cdot s^{1/2}/mV^{-1/2}$) + 0.44. The peak current was proportional to the NRT concentration with a linear equation: i_p (μA) = 25.95·[NRT](mM)+ 0.93; r^2 = 0.998 in the range $5 \cdot 10^{-5}$ M to $1 \cdot 10^{-3}$ M, with a detection limit of $5 \cdot 10^{-6}$ M, calculated as the NRT concentration that gives a signal corresponding to three times the standard deviation of estimate. The precision (inter-electrode) measured in terms of RSD was 0.8% for a concentration of $2.5 \cdot 10^{-4}$ M of NRT, when different electrodes are used.

Differential pulse voltammetry was also used as quantitation technique and a linear calibration curve i_p (μA) = 32.64·[NRT](mM) + 1.06; r^2 = 0.993) was obtained between $1 \cdot 10^{-5}$ M and $1 \cdot 10^{-3}$ M, so it is shown as a more sensitive technique than cyclic voltammetry as expected. The limit of detection in this case was 0.9 μM, calculated as the NRT concentration that gives a signal corresponding to three times the standard deviation of estimate. A precision (inter-electrode) of 0.6% (RSD) was obtained when using 5 different SPEs to measure a 0.25 mM concentration of NRT.

The monitoring of spectral changes occurred during the voltammetric oxidation of NRT can be easily carried out by UV-VIS Spectroelectrochemistry and it was *in situ* evaluated for the very first time in this work according to our knowledge. Naratriptan (colourless solution) is transformed to a diindole based dimer after electrochemical oxidation (yellowish colour solution) leading to an increase of a broad absorbance band between 300 and 430 nm with a maximum intensity at around 320-360 nm (Figure 3). The corresponding voltabsorptogram obtained at 320 nm is shown in Figure 2B. Absorbance does not change the initial zero value up to the overpotential is positive enough to oxidise NRT at around +0.65 V. From this potential upwards, absorbance increases until the oxidation is completed and it does not decrease in the backward scan, indicating that an irreversible oxidation of naratriptan has taken place in this potential range. The derivative voltabsorptogram at 320 nm (Figure 2A, red colour line) exhibits a full correlation with the cyclic voltammogram indicating that the two signals are related to the same process. Video S1 is available as Supporting Information showing the voltabsorptogram and the derivative voltabsorptogram of Naratriptan in real time at untreated screen-printed carbon electrodes. A calibration curve with a linear range between $5 \cdot 10^{-4}$ and $5 \cdot 10^{-3}$ M was recorded with the UV/VIS spectroelectrochemical technique following the equation: A (a.u.) = 0.12 [NRT](mM) + 0.07; r^2 = 0.99. The limit of detection was 0.1 mM, calculated as the NRT concentration that gives a signal corresponding to three times the standard deviation of estimate. A precision (inter-electrode) of 10.1% (RSD) was obtained when using 3 different electrodes to measure a 1 mM concentration of NRT. As expected, the limit of detection using UV/VIS spectroelectrochemistry is higher than the voltammetric techniques as the UV/VIS detection is typically less sensitive. However, the detection by measuring the

absorbance of the oxidation product increases the selectivity of the detection. This could be used to discriminate interfering species with oxidation potentials close to naratriptan but whose oxidation products do not absorb in the same range of wavelengths.

The same *in situ* characterization process was performed by time resolved Raman Spectroelectrochemistry. In this case, no electrochemical oxidation of Naratriptan is performed and electrochemistry is used to produce *in situ* a SERS substrate based on a screen printed silver electrode. As observed in the Figure 4A, a cyclic voltammogram was carried out from +0.3 V to -0.4 V in presence of NRT using 0.1 M KCl as electrolyte solution. At the initial potential, the silver working electrode is electrochemically oxidized producing silver ions that in presence of chloride ions precipitate as AgCl (s) in the surface of the electrode increasing the roughness and porosity but no Raman signal is detected for Naratriptan drug. Later AgCl (s) is reduced at a more negative potential of -0.25 V generating *in situ* new metallic silver (Ag^0) electrodeposited in the electrode surface. Simultaneously as Raman spectra are recorded during cyclic voltammetry a Raman signal fingerprint corresponding to Naratriptan is observed due to the SERS effect attributed to this new metallic electrode surface when a negative potential such as -0.3 V is reached. Therefore, a chemical interaction between Naratriptan and freshly reduced metallic silver particles is assumed. In the backward scan when silver is oxidized again the Raman signal is lost. *In situ* Raman monitoring of the process is very useful since there is a clear evolution of the Raman spectra during the electrochemical voltammogram. Using a scan rate of 50 mV/s and an integration time of 2 s, it means we can have a Raman spectra every 100 mV and we were able to know that the SERS effect is detected when silver is electrochemically reduced (between -0.2 V and -0.4 V). Experimental spectrum shown in Figure 4A was recorded

at -0.35 V. If it were needed, a faster scan rate and a shorter integration time could be applied so the Raman spectra could be obtained at a gap lower than 100 mV. This option would be very attractive in more complex applications or to elucidate reaction mechanisms. Figure 4A also shows the predicted spectrum of naratriptan between 600 and 1700 cm^{-1}. Experimental and predicted spectra are well correlated, although the intensity ratio between bands is different, suggesting that the interaction with silver plays an important role in those vibrations. The higher intensity of both spectra was observed for the band at 1539 cm^{-1}, which can be tentatively assigned to C-C aromatic ring chain vibrations as observed in the predicted vibrations shown in Video S2. The peak intensity of the Raman signal at 1539 cm^{-1} at a specific potential of -0.35 V when it is maximum was used for detection purposes. A linear calibration curve between $2.5 \cdot 10^{-5}$ M and $2.5 \cdot 10^{-4}$ M was obtained following the linear equation: I (counts) = 52.52 [NRT] (µM) – 192.8. A good precision (RSD of calibration slopes=7.6%, n= 3) and a limit of detection of 1.2 µM were obtained. A precision (inter-electrode) of 9.2% (RSD) was obtained when using 5 different electrodes to measure a 100 µM concentration of NRT. These analytical figures of merit are similar to those obtained with voltammetric techniques, but Raman detection increases significantly the selectivity because the Raman spectra are specific to molecules (it is a fingerprint technique) and typically consist of numerous narrow Raman band that can be used for quantification. Figure 4B shows the increasing intensity of the Raman signal at this specific frequency with increasing concentrations of NRT. Even a more sensitive detection could be obtained by increasing the integration time at the specific potential where SERS effect is highlighted. Therefore, *in situ* Raman allows to perform quantitative analysis that would be very difficult to carry out when using *ex situ* Raman technique of non-homogeneous

electrode surfaces, because the response depends on the sampling area after and before the electrochemical treatment and no real time and repeatable information is obtained.

4. Conclusions

Cyclic voltammetry and differential pulse voltammetry have been demonstrated to be simple and efficient methods for the electrochemical determination of Naratriptan in the surface of untreated screen-printed carbon electrodes. A new approach for the *in situ* characterization of Naratriptan oxidation by time resolved UV-VIS Spectroelectrochemistry is introduced. It easily allows us to confirm in real time the solution colour change (colourless to yellowish) corresponding to the electrochemical process. Raman Spectroelectrochemistry of Naratriptan is observed due to *in situ* generation of cost effective silver based SERS substrates and quantitative analysis is performed. The use of miniaturised screen-printed carbon and silver electrodes allows a fast and easy analysis with a simple experimental setup for both spectroelectrochemical techniques in comparison with the use of conventional electrodes. Furthermore, the use of spectroelectrochemical techniques allows to increase the selectivity of the detection of naratriptan.

References

[1] N. Ramadan, V. Skljarevski, L. Phebus, K. Johnson, 5-HT1F receptor agonists in acute migraine treatment: a hypothesis, Cephalalgia. 23 (2003) 776–785. doi:10.1046/j.1468-2982.2003.00525.x.

[2] F.D. Sheftell, A.M. Rapoport, S.J. Tepper, M.E. Bigal, Naratriptan in the Preventive Treatment of Refractory Transformed Migraine: A Prospective Pilot Study, Headache J. Head Face Pain. 45 (2005) 1400–1406. doi:10.1111/j.1526-4610.2005.00273.x.

[3] K.. Altria, R. McLean, Development and optimisation of a generic micellar electrokinetic

capillary chromatography method to support analysis of a wide range of pharmaceuticals and excipients, J. Pharm. Biomed. Anal. 18 (1998) 807–813. doi:10.1016/S0731-7085(98)00219-2.

[4] B. Pasquini, S. Orlandini, M. Del Bubba, E. Bertol, S. Furlanetto, The successful binomium of multivariate strategies and electrophoresis for the Quality by Design separation of a class of drugs: the case of triptans, Electrophoresis. 36 (2015) 2650–2657. doi:10.1002/elps.201400472.

[5] K. Vishwanathan, M.G. Bartlett, J.T. Stewart, Determination of antimigraine compounds rizatriptan, zolmitriptan, naratriptan and sumatriptan in human serum by liquid chromatography/electrospray tandem mass spectrometry, Rapid Commun. Mass Spectrom. 14 (2000) 168–172. doi:10.1002/(SICI)1097-0231(20000215)14:3<168::AID-RCM861>3.0.CO;2-9.

[6] B.. Duléry, M.. Petty, J. Schoun, M. David, N.. Huebert, A method using a liquid chromatographic-electrospray-mass spectrometric assay for the determination of antimigraine compounds: preliminary pharmacokinetics of MDL 74,721, sumatriptan and naratriptan, in rabbit, J. Pharm. Biomed. Anal. 15 (1997) 1009–1020. doi:10.1016/S0731-7085(96)01955-3.

[7] K.A. Rawat, K.R. Surati, S.K. Kailasa, One-pot synthesis of gold nanoparticles by using 4-aminoantipyrine as a novel reducing and capping agent for simultaneous colorimetric sensing of four triptan-family drugs, Anal. Methods. 6 (2014) 5972-5980. doi:10.1039/C4AY00098F.

[8] C. Velasco-Aguirre, A. Álvarez-Lueje, Voltammetric behavior of naratriptan and its determination in tablets, Talanta. 82 (2010) 796–802. doi:10.1016/j.talanta.2010.05.058.

[9] S. Bernad, W. Mäntele, An innovative spectroelectrochemical reflection cell for rapid protein electrochemistry and ultraviolet/visible/infrared spectroscopy, Anal. Biochem. 351 (2006) 214–218. doi:10.1016/j.ab.2005.12.024.

[10] C.A. Schroll, S. Chatterjee, W.R. Heineman, S.A. Bryan, Semi-Infinite Linear Diffusion Spectroelectrochemistry on an Aqueous Micro-Drop, Anal. Chem. 83 (2011) 4214–4219. doi:10.1021/ac200551n.

[11] P.A. Flowers, D.A. Blake, Submicroliter Electrochemistry and Spectroelectrochemistry Using Standard Electrodes and a Polymer Electrolyte Salt Bridge, Anal. Chem. 85 (2013) 3059–3063. doi:10.1021/ac303712v.

[12] C.N. Hernández, M.B.G. García, D.H. Santos, M.A. Heras, A. Colina, P. Fanjul-Bolado, Aqueous UV–VIS spectroelectrochemical study of the voltammetric reduction of graphene oxide on screen-printed carbon electrodes, Electrochem. Commun. 64 (2016) 65–68.

doi:10.1016/j.elecom.2016.01.017.

[13] N. González-Diéguez, A. Colina, J. López-Palacios, A. Heras, Spectroelectrochemistry at Screen-Printed Electrodes: Determination of Dopamine, Anal. Chem. 84 (2012) 9146–9153. doi:10.1021/ac3018444.

[14] A. Habekost, Rapid and sensitive spectroelectrochemical and electrochemical detection of glyphosate and AMPA with screen-printed electrodes, Talanta. 162 (2017) 583–588. doi:10.1016/j.talanta.2016.10.074.

[15] C. Fernández-Blanco, Á. Colina, A. Heras, UV/Vis spectroelectrochemistry as a tool for monitoring the fabrication of sensors based on silver nanoparticle modified electrodes, Sensors (Switzerland). 13 (2013) 5700–5711. doi:10.3390/s130505700.

[16] Y.-C. Liu, C.-C. Yu, S.-F. Sheu, Improved surface-enhanced Raman scattering on optimum electrochemically roughened silver substrates, Anal. Chim. Acta. 577 (2006) 271–275. doi:10.1016/j.aca.2006.06.062.

[17] Y.-C. Liu, C.-C. Yu, S.-F. Sheu, Low concentration rhodamine 6G observed by surface-enhanced Raman scattering on optimally electrochemically roughened silver substrates, J. Mater. Chem. 16 (2006) 3546-3551. doi:10.1039/b609417a.

[18] A.M. Robinson, S.G. Harroun, J. Bergman, C.L. Brosseau, Portable Electrochemical Surface-Enhanced Raman Spectroscopy System for Routine Spectroelectrochemical Analysis, Anal. Chem. 84 (2012) 1760–1764. doi:10.1021/ac2030078.

[19] L. Zhao, J. Blackburn, C.L. Brosseau, Quantitative Detection of Uric Acid by Electrochemical-Surface Enhanced Raman Spectroscopy Using a Multilayered Au/Ag Substrate, Anal. Chem. 87 (2015) 441–447. doi:10.1021/ac503967s.

[20] P. Fanjul-Bolado, D. Hernández-Santos, P.J. Lamas-Ardisana, A. Martín-Pernía, A. Costa-García, Electrochemical characterization of screen-printed and conventional carbon paste electrodes, Electrochim. Acta. 53 (2008) 3635–3642. doi:10.1016/j.electacta.2007.12.044.

[21] M. Valiev, E.J. Bylaska, N. Govind, K. Kowalski, T.P. Straatsma, H.J.J. Van Dam, D. Wang, J. Nieplocha, E. Apra, T.L. Windus, W.A. de Jong, NWChem: A comprehensive and scalable open-source solution for large scale molecular simulations, Comput. Phys. Commun. 181 (2010) 1477–1489. doi:10.1016/j.cpc.2010.04.018.

[22] D.M. York, M. Karplus, A Smooth Solvation Potential Based on the Conductor-Like Screening

CAPTIONS FOR FIGURES AND TABLES

Figure 1. Naratriptan chemical structure and its oxidation procedure to arise the yellowish colour diindole based product.

Figure 2. (A) Comparison between derivative voltabsorptogram of NRT at 320 nm (red line) and the corresponding cyclic voltammogram (blue line) at 50 mV/s in 0.1 M Britton-Robinson pH 3.0 buffer solution; (B) Voltabsorptogram at 320 nm for the electrochemical oxidation of Naratriptan.

Figure 3. Evolution of UV-VIS reflection spectra (in absorbance units) during electrochemical oxidation of Naratriptan using untreated screen-printed carbon electrodes.

Figure 4. (A) Cyclic voltammogram for roughening of screen printed silver electrodes in presence of Naratriptan using 0.1 M KCl electrolyte solution. Inset: Raman spectrum (background subtracted) of Naratriptan obtained at -0.35 V showing the great SERS effect and the predicted spectrum using DFT calculations. (B) Raman spectra (1490-1600 cm^{-1} range) for several concentrations of Naratriptan recorded at -0.35 V during the electrochemical activation of screen printed silver electrodes.

Figure 1

Figure 1

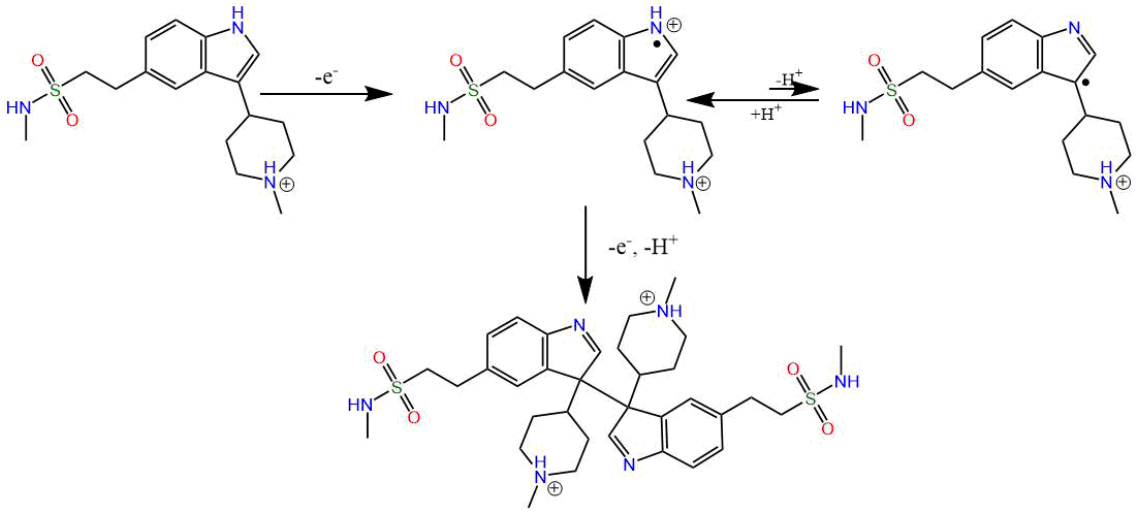
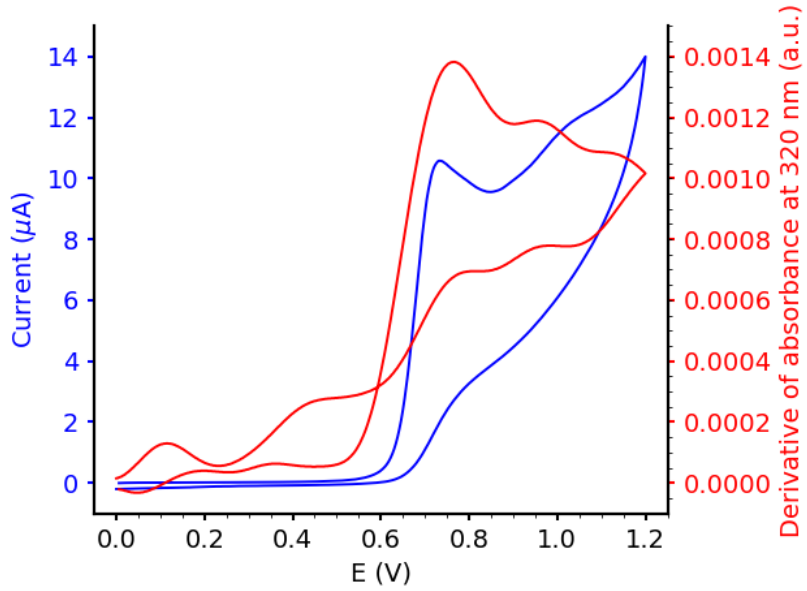


Figure 2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6
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10
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14
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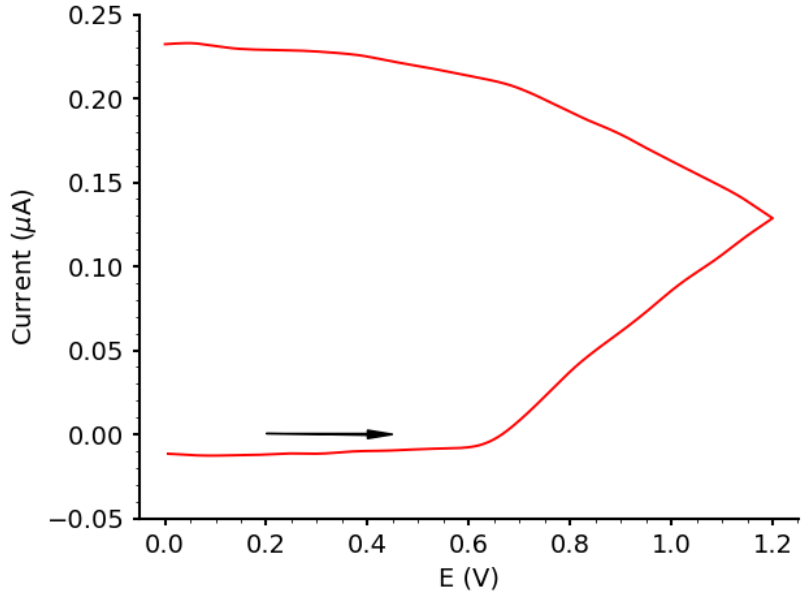
0.0002
0.0004
0.0006
0.0008
0.0010
0.0012
0.0014
0.0
0.2
0.4
0.6
0.8
1.0
1.2

A)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0.25
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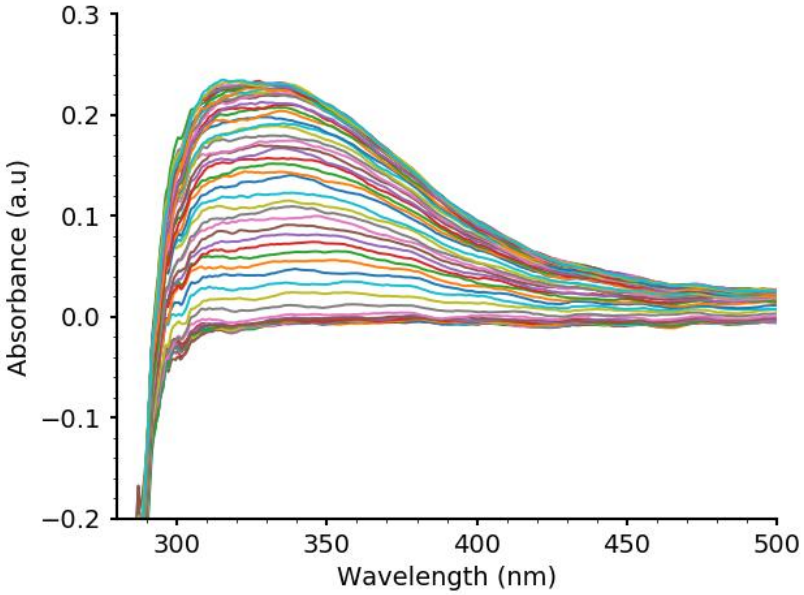
0.6
0.8
1.0
1.2

B)

Figure 3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350
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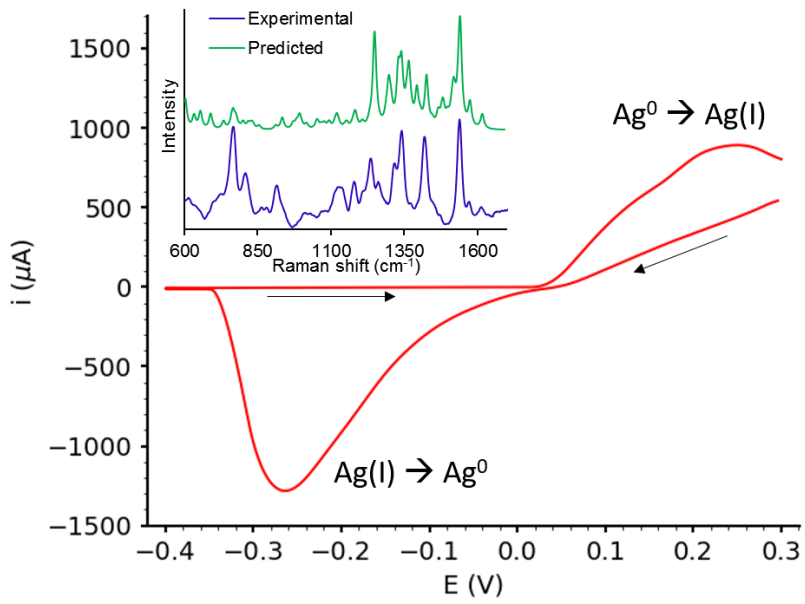
450
500
Wavelength (nm)

Figure 4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Predicted
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Ag(I) → Ag⁰
i (μA)
E (V)
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1000
500
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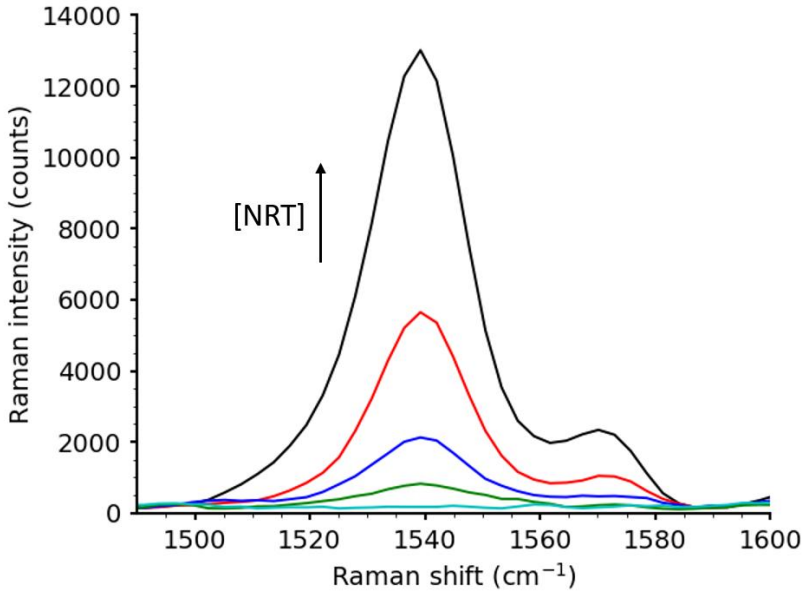
0.1
0.2
0.3

A)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Raman shift (cm⁻¹)
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2000
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1500
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1560
1580
1600

B)