A benzocaine-induced local near-surface pH effect : influence on the accuracy of voltammetric cocaine detection

A Benzocaine-Induced Local Near-Surface pH Effect: Influence on the Accuracy of Voltammetric Cocaine Detection

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Abstract: This work reports on a local induced near-surface pH effect (pH_S), due to the presence of one analyte, leading to an influence or even suppression of redox signals of a second analyte present in solution. This concept and its impact on voltammetric sensing is illustrated by focusing on the detection of cocaine in the presence of the common adulterant benzocaine. An in-depth study on the occurring interference mechanism and why it occurs for benzocaine specifically and not for other adulterants was performed through the use of multiple electrochemical strategies. It was concluded that the potential shift and loss of intensity of the square-wave voltammetric cocaine signal in the presence of benzocaine was caused by a local pH_S effect. A cathodic pretreatment strategy was developed to nonetheless allow accurate cocaine detection. The gathered insights are useful to explain unidentified phenomena involving compounds with properties similar to benzocaine in voltammetric electroanalysis.

Introduction

The production, trafficking and consumption of drugs of abuse is a growing issue on a global scale. The United Nations estimated that 5.4 % of the world population (15-64 age group) used drugs in the year 2018.[1] More alarmingly, the global amount of drug-related deaths was estimated at 585,000, a number which is more than double the amount of deaths in 1990 (270,000).[1-2] Illegal drug trafficking causes next to this impact on health also a significant damage to the economy. With the drug trafficking market being worth around 550 billion US dollars in the year 2014, it was only preceded by the counterfeiting market concerning the net value of transnational crimes.[3]

Cocaine is a highly addictive stimulant drug which forms a threat to public health. On a short-term basis, undesirable effects like an increased heart rate, blood pressure, and respiration rate could occur, while after long-term use the addiction might cause a state of lethargy, extreme tiredness, and depression when the cocaine consumption stops.[4]

The development of fast and reliable methods for on-site cocaine detection is therefore of greater importance than ever before, in order to help reduce the production, trafficking and consumption. The most common on-site screening method for cocaine is the Scott color test, which is cheap, but also highly unreliable on both sensitivity and specificity aspects.[5]

In our previous work, we presented the great advantage of electrochemical approaches over the use of classical color tests for the on-site screening of cocaine, concerning accuracy.[5a] In addition, electrochemical strategies are fast, robust, simple in use, cost-efficient and easily miniaturized. Using disposable screen printed electrodes (SPEs) allows fast analysis for multiple samples.

The presence of several adulterants of cocaine have shown to cause an undesirable suppression effect on the cocaine signal using neutral pH 7 phosphate buffers, encouraging us to develop an optimized strategy using alkaline pH 12 buffer, removing these effects.[5a, 6]

However, there is one adulterant that has a negative effect on voltammetric cocaine detection in both pH 7 and the optimized pH 12 condition, leading to a false negative result for cocaine presence. This adulterant is benzocaine, also referred to as 4-aminobenzoic acid ethyl ester. In Europe, it is the fifth mostly encountered adulterant behind levamisole, phenacetin, caffeine and lidocaine.[7] In 20% of the studied countries, benzocaine is even one of the top three adulterants used for cocaine adulteration.[7] Benzocaine is a topical anesthetic agent with pain-relieving properties commonly employed in oral ulcers.[8] Moreover, it is well-known for its analgesic potency in oral and pharyngeal mucous membranes including mouth cancers, dental and otic discomforts, and local anesthesia in surgical procedures.[9] Over-dosing benzocaine could induce an irregular heartbeat and lung problems, but it is perfectly safe to use in normal dosage.[10]

In contrast to the other adulterants, a voltammetric detection in pH 12 does not provide a solution for benzocaine, as a shift of the cocaine signal to more positive potentials occurs along with a loss of signal intensity. This suggests a different mechanism is taking place compared to the other studied compounds in our earlier work.[6] The subsequent goal of this paper is to identify and clarify the mechanism behind the benzocaine interference and to provide a solution to allow reliable electrochemical cocaine detection in the presence of benzocaine.

Results and Discussion

Outlining the analytical problem

The presence of benzocaine (Figure 1) in cocaine samples has an interfering effect on the cocaine square-wave voltammetry (SWV) signal, therefore hindering the (reliable)

voltammetric detection of cocaine in street samples. SWV was performed on binary mixtures (0.5 mM cocaine:0.5 mM benzocaine) in both pH 7 and pH 12 buffer solutions in order to illustrate the exact nature of this problem. 87 % of the street samples encountered in Belgium have a benzocaine to cocaine molar ratio lower than 1, making the chosen 1 to 1 ratio one of the extreme cases of benzocaine adulteration. This ratio is, thus, rather rare, with street samples usually containing less benzocaine. The average benzocaine to cocaine molar ratio was found to be approximately 1 to 4 (data available from National Institute of Criminalistics and Criminology for the period 2013-2017). American and Brazilian studies also report on low average quantities of benzocaine in cocaine samples, ranging from 0.6 to 13.7 wt %. The samples containing the highest amount of benzocaine in these studies approximates the 1 to 1 cocaine:benzocaine molar ratio range used in this work.[11]

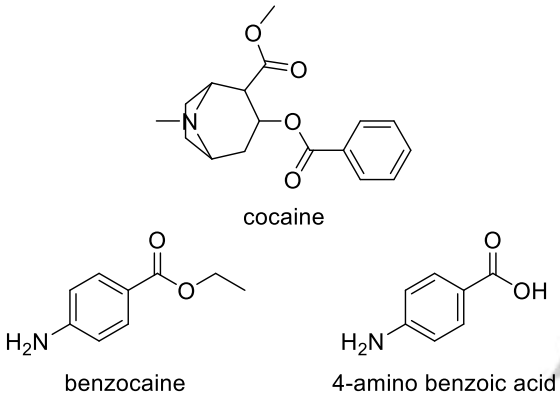

Figure 1. Chemical structures of cocaine, benzocaine and 4-aminobenzoic acid.

Figure 2 A shows that the cocaine signal (black line with E_p at 0.98 V) is suppressed in a mixture with benzocaine at pH 7 (blue line). The signal present at 1.25 V (red line) is attributed to an impurity on the electrode. Figure 2 B indicates that at pH 12 the signal for cocaine is detectable in a mixture with benzocaine (blue line), but at a different peak potential, i.e. 0.94 V, and with a lower peak current intensity (drop from approximately 8 µA to 2 µA). Usually, the cocaine signal is detectable with a peak potential of 0.83 V in pH 12, so there is a significant shift of ca. 110 mV of the cocaine peak potential in mixture with benzocaine. Therefore, these effects pose a problem for correct cocaine identification when using a software script based on peak potentials if no correction factors are implemented.

The question remains: what is causing this two-fold effect, i.e. cocaine peak suppression and potential shift by benzocaine? Our previous work showed a suppression effect occurring in pH 7 when specific adulterants were present in the cocaine sample. However, such effect was not occurring using pH 12 buffer. Furthermore, no peak potential shift was observed either. Therefore, it is expected that none of the mechanisms describe the phenomenon for benzocaine. In the following parts, a thorough assessment was made to identify the underlying mechanism.[6]

Identifying the fundamental problem

The peak potential shift of cocaine to more positive potential values (Figure 2 B) in the presence of benzocaine is a unique phenomenon. The hypothesis of a local near-surface pH effect explaining it was proposed since pH changes do typically cause peak potential shifts for redox-active species, among which several drugs. The occurrence of a local pH effect near the electrode surface during potentiostatic experiments, changing the electrochemical properties of target analytes, is a theory first presented by A.T. Kuhn and C.Y. Chan. They published a widely cited paper in 1983 addressing the effects of electrode processes which include the release or consumption of protons.[12] This paper describes a clear deviation of the local pH near the electrode surface by introducing the concept 'pH_S' (near-surface pH). Results of multiple studies indicate that this effect can be relatively large. It was found to be less prominent in buffered systems, but it still occurs.[12]

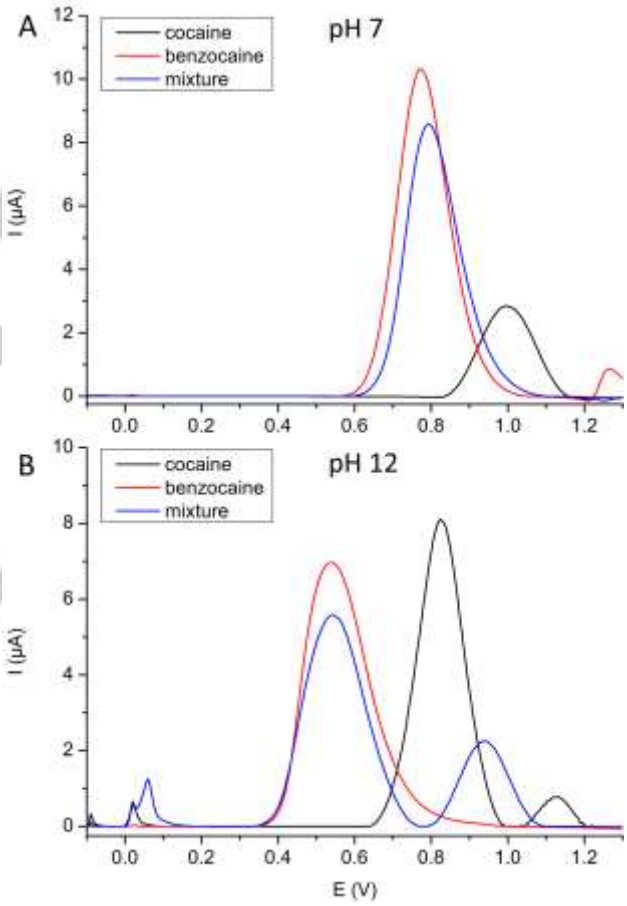

Figure 2. SWVs of cocaine, benzocaine, and a binary mixture of cocaine and benzocaine (0.5:0.5 mM) in a pH 7 (A) and a pH 12 (B) buffer solution.

Given the shift in potential, this hypothesis was examined by performing SWV on cocaine and cocaine:benzocaine mixtures at different pH values, cocaine:benzocaine ratios and buffer concentrations.

The possibility of electropolymerization of benzocaine onto the electrode surface, was also examined, because of its structural resemblance to 4-amino benzoic acid, which is a well-known monomer. However, our findings (Section S2.1 and Figure S1 in the *Supporting Information*) do not indicate electropolymerization for benzocaine and is therefore not the reason for the

benzocaine induced interference. In addition, scan rate studies using linear sweep voltammetry indicate a diffusion-controlled oxidation process occurs for benzocaine, both in pH 7 and pH 12 conditions (Section S2.1 and Figure S2). Benzocaine incubation experiments using SWV (Section S2.1 and Figure S3) also show hardly any benzocaine adsorbed at the surface. Therefore, there is no evidence for the adsorption of a benzocaine-related compound blocking the electrode surface.

A local pH_S effect causing the apparent suppression of cocaine by benzocaine

During oxidation of benzocaine (E_P = 0.78 V for pH 7 and 0.55 V for pH 12), two electrons and two protons are released during the oxidation of the primary amine of the aniline group to a secondary amine with the protons acidifying the region near the electrode surface.[13] Therefore, benzocaine has the intrinsic potential to create a local pH effect. In neutral to alkaline conditions, the secondary amine oxidizes further to a nitro group, releasing three more protons.[14] Even at the oxidation potential of cocaine (E_P = 0.98 V for pH 7 and 0.83 V for pH 12), benzocaine is oxidized and more protons are being released near the electrode surface, causing the signal for cocaine to shift because of this local pH effect. This effect might be increased by the intrinsic acidic behavior of benzocaine (pK_a = 2.51 and pH in 0.1 M benzocaine solution in water = 1.53).[15]

Figure 3 clearly illustrates the lack of a clear cocaine electrochemical signal when going to solutions with a pH value of 6 or below, indicating cocaine becomes electrochemically inactive in this region (using graphite SPEs), causing the currents to drop near and below the detection limit. This hints that, due to a local pH_S effect, the pH can potentially drop below the value of 6, causing the absence of the cocaine signal in mixture with benzocaine in pH 7 solutions. Therefore, the lack of cocaine signal is due to an 'apparent' suppression. In addition, changing the pH also causes a clear peak potential shift. Table S1 in the *Supporting Information* shows the registered peak potential and normalized peak current values for the cocaine signal at all studied pH values.

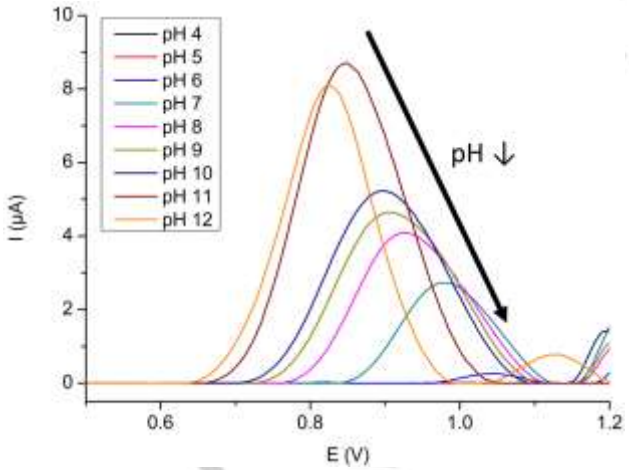

Figure 3. Zoomed in SWV of 0.5 mM cocaine at different pH values (4-12) using PBS.

To further evidence this hypothesis of a local pH_S effect, mixtures of cocaine and benzocaine with different ratios have been prepared and analyzed with SWV in both a pH 7 and a pH 12 buffer. A higher benzocaine concentration is expected to cause a larger local pH_S effect and thus a larger peak potential shift and current drop. Indeed, this is observed in the data shown in Figure 4.

Figure 4 A shows that even a low concentration of benzocaine already has a large effect on the presence of the cocaine signal in a pH 7 buffer, making it absent from the total electrochemical fingerprint. In pH 12 a similar effect causes peak potentials to shifts and peak currents to drop, however, not leading to the total removal of the signal (Figure 4 B). This was expected since the original pH of this buffer is high enough to avoid the local pH to drop below the value at which the redox process becomes invisible in the given potential window. Adding more benzocaine leads to a more prominent shift and current drop. Comparing this data to the data in Figure 3 and Table S1 elucidates a strong correlation between relative benzocaine concentration and pH. The peak potential and normalized peak current values for cocaine in these different mixtures are shown in Table S2.

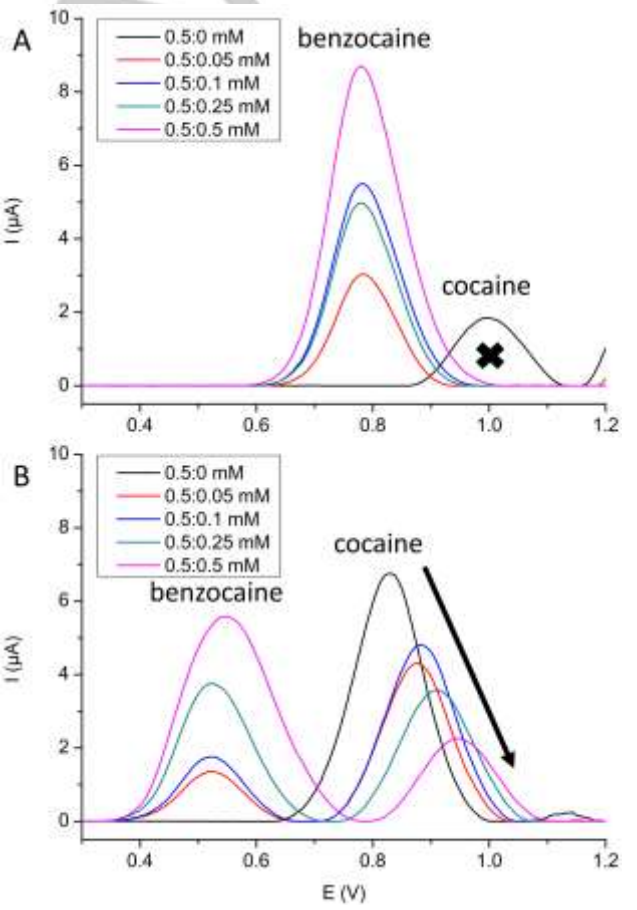

Figure 4. Zoomed in SWVs of cocaine:benzocaine binary mixtures with different concentration ratios in (A) a pH 7 and (B) a pH 12 buffer.

A similar potential shift and current drop is observed for the cocaine signal compared to the data presented in Figure 3 and Table S1. The equimolar mixture containing 0.5 mM of cocaine and benzocaine for instance shows a close resemblance with the signal of pH 7 in Figure 3 and Table S1 (0.95 V and 0.33 relative current intensity vs 0.98 V and 0.33 relative current intensity, respectively). In accordance, the 0.5:0.25, 0.5:0.1,

0.5:0.05 and 0.5:0 mM mixtures correspond to the signals of pH 8-9, 10-11, 10-11 and 12 from Figure 3, respectively.

A quantitative approximation of the correlation between pH and relative benzocaine concentration is made for the E_P and I_P quantities using the Pearson correlation coefficient. It is a measure of the linear correlation between two different variables. It has a value between +1 and −1, where +1 stands for perfect positive linear correlation, 0 for no linear correlation, and −1 for negative linear correlation. The Pearson coefficients calculated here are an approximation because we have discrete data sets. Therefore, only the E_P and I_P values with the closest match of a specific pH data point and a specific concentration ratio data point are considered. The linked data points used for the determination of the Pearson coefficient are shown in Table 1.

Using the corresponding E_P and I_P values, the Pearson coefficient to quantitatively describe the correlation between concentration ratio and pH was found to be 0.96 and 0.99 for E_P and I_P, respectively. With a maximum possible value of 1, these values indicate there is indeed a strong positive correlation.

Table 1. The concentration ratio data points and corresponding pH data points linked for the calculation of the Pearson correlation coefficient for the E_P and I_P values.

Cocaine:benzocaine ratio (mM)		pH
0.5:0	linked to	12
0.5:0.05	linked to	10
0.5:0.1	linked to	10
0.5:0.25	linked to	9
0.5:0.5	linked to	7

Since several of the other adulterants of cocaine also release protons after oxidation, the effect of two of these compounds on the cocaine signal was studied, although no clear interfering effect for cocaine detection was observed for these compounds in our previous work. Phenacetin and lidocaine were chosen for the following reasons: (i) phenacetin has a pK_a of 2.2,[16] which is comparable to benzocaine, (ii) lidocaine has a pK_a of 8.0,[16] which is much higher compared to benzocaine, (iii) both compounds release less protons (one for phenacetin[17] and two for lidocaine[18]) compared to the five of benzocaine. The combination of low pK_a value and high amount of released protons during oxidation makes benzocaine indeed a unique compound among the adulterants of cocaine. The effect of benzocaine is therefore expected to be exceptional, explaining why such effect was not observed with other adulterants.

In order to study the influence of phenacetin compared to benzocaine, analogue experiments to the ones from Figure 4 were performed with phenacetin instead of benzocaine.

The results in Figure 5 A show a slight effect of phenacetin on the cocaine signal in pH 7 buffer. The cocaine peak current drops gradually from 2.1 to 1.5 µA when more phenacetin is added, while the peak potential rises gradually from 0.99 to 1.01 V. This effect is only small, causing no complications for the automated detection of cocaine using compound identification scripts. This slight change of E_P and I_P corresponds to only a minor pH_S-induced effect as can be derived from Figure 3 and Table S1. The E_P and I_P values for cocaine in the 0.5:0.5 mM cocaine:phenacetin mixture still correspond more to the characteristics of the cocaine signal in pH 7 buffer compared to pH 6, proving the pH has not changed significantly as was the case with benzocaine, where the cocaine signal disappeared in the mixtures (Figure 4 A). Figure 5 B shows no clear trend using a pH 12 buffer. This is explained by the fact that the change from pH 12 to 11 is less dramatic on the cocaine signal compared to the change from pH 7 to 6. Only a shift of 30 mV and a current increase of 7 % occurs in this case (Figure 3 and Table S1). For phenacetin, which has a similar pK_a value as benzocaine, however produces only one-fifth of the protons of benzocaine during oxidation, a similar local pH effect occurs, albeit less significant, posing no issues to detect cocaine using the chosen buffers of pH 7 and 12.

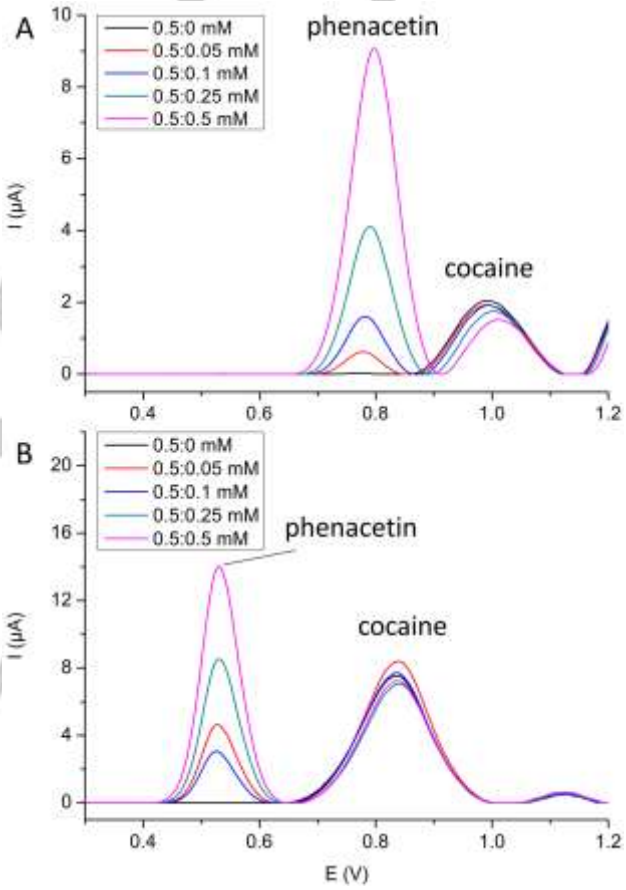

Figure 5. Zoomed in SWVs of cocaine:phenacetin binary mixtures with different concentration ratios in (A) pH 7 and (B) pH 12 buffer.

The same experiment was performed for lidocaine (Figure 6), which has a higher pK_a value and releases two protons during oxidation. No clear trend is observed using both pH 7 and pH 12 buffers. The peak currents are slightly more difficult to compare since the lidocaine signal overlaps partially with the cocaine signal, causing an offset of the peak current of cocaine in the 0.5:0.5 mM sample. However, for the other cocaine:lidocaine ratio samples, the peak current for cocaine is always comparable, for both pH 7 and pH 12 buffer.

In order to produce a significant local pH_S effect, it is required to have a compound in mixture with cocaine, which both has a low pK_a value and releases multiple protons during the oxidation process.

This effect makes the SWV signal of cocaine invisible in the presence of benzocaine as the pH locally drops below pH 6 (Figure 3), leading to false negatives. This is confirmed by an experiment in which cocaine is replaced by a molecule which does produce detectable oxidation signals at lower pH-values, for example MDMA (chemical structure shown in Figure S4 in the *Supporting Information)*.[19] Even with a local drop in pH, the original fingerprint of MDMA should be retained.

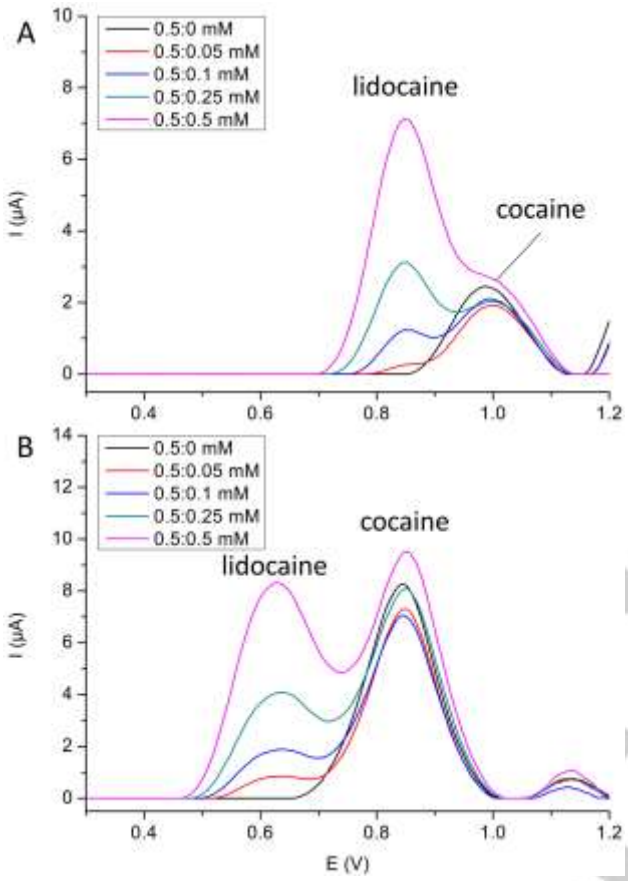

Figure 6. Zoomed in SWVs of cocaine:lidocaine binary mixtures with different concentration ratios in (A) pH 7 and (B) pH 12 buffer.

Therefore, analogue experiments to those of Figure 3 and 4 were performed with MDMA instead of cocaine. The pH-dependent response of 0.5 mM MDMA is shown in Figure 7 A. Clearly, at all pH values the characteristic P1 process is observed. P1 is related to the transition of the aromatic group to a radical cation, while P2 (only visible for pH ≥ 10 in Figure 7 A) is related to the oxidation of the secondary amine group to a primary amine and formaldehyde in aqueous solutions.[19]

Figure 7 B illustrates that, in the presence of benzocaine, the MDMA P1 signal is always visible. A peak potential shift and a lower intensity of the MDMA P1 signal is observed when more benzocaine is added to the solution. These observations again evidence a strong correlation with a change of pH (Figure 7 A). For instance, the MDMA signal for the 0.5:0.5 mM mixture with benzocaine in Figure 7 B (E_P = 1.12 V and I_P = 7.0 µA) is located closely to the peak of pure MDMA in pH 5 buffer (Figure 7 A), E_P = 1.11 V and I_P = 4.6 µA), with the signals of the remaining ratios evolving gradually from the pH 5 to 7 situation when less benzocaine is added. Also the peak currents change in correspondence to what was found for the pH study of MDMA. These findings indicate the electrode surface is still accessible for oxidation reactions to occur for substances diffusing from the bulk. Therefore, a blockage of the electrode surface due to strong adsorption of benzocaine or the formation of a strong adsorbate on the surface during the process is unlikely.

Another indication that a local pH_S effect is occurring is provided by altering the buffer strength of the solution. Using a more concentrated buffer should lead to less significant pH effects in the solution. This was indeed the case for a five-fold more concentrated buffer, leading to only a slight pH_S effect, as is shown in section S2.2 and Figure S5 in the *Supporting Information*.

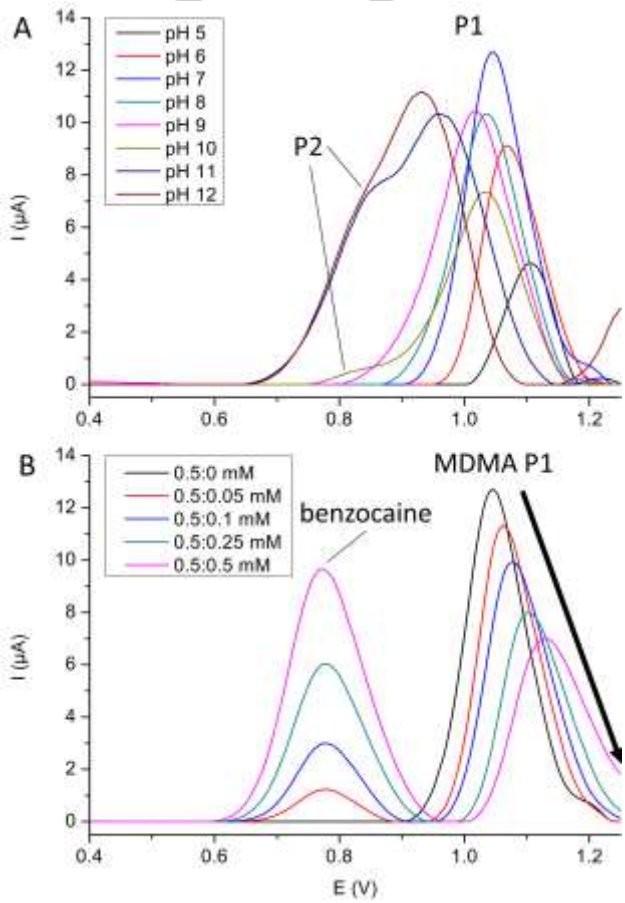

Figure 7. SWVs of (A) 0.5 mM MDMA in a PBS buffer with pH ranging from 5 to 12; (B) mixtures of MDMA and benzocaine with different concentration ratios using PBS pH 7.

In addition to these indirect approaches through voltammetric methods, more conclusive evidence was gathered through a more direct determination of the pH using fluorescence-based microscopy. Although the pH_S effect is indeed a local effect near the electrode surface, extending the timeframe of the benzocaine oxidation process would result in an intensification of the effect, but, more importantly, also in an extension of this effect into the bulk of the measured droplet. Therefore, a chronamperometry measurement was performed at a fixed potential of 1.00 V in pH 7 buffer for 30 minutes. A pH-

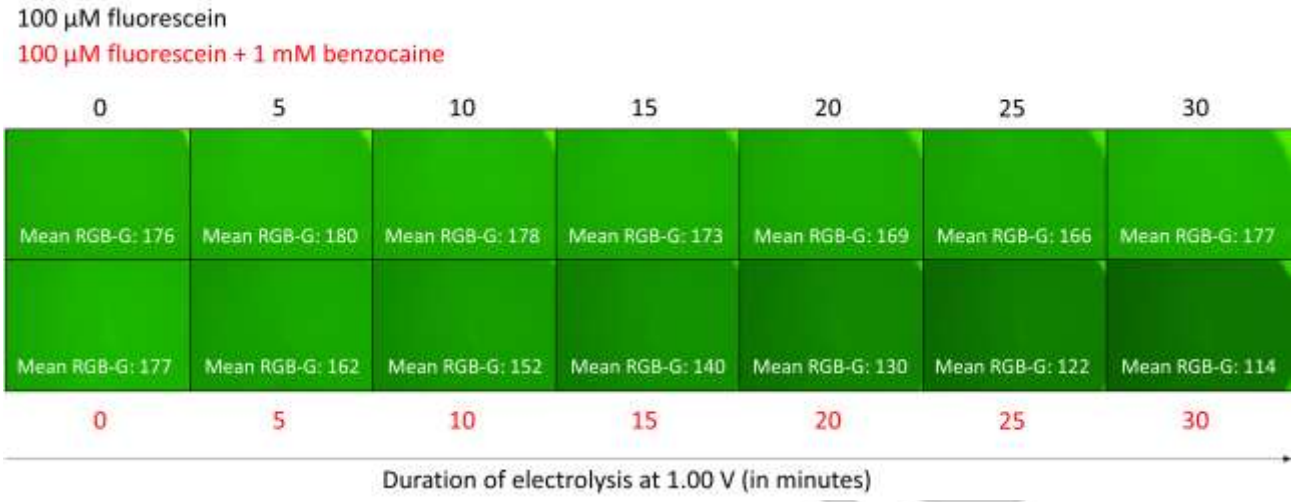

Figure 8. Fluorescence microscopic images of the SPE surface with corresponding average green light intensity during a chronoamperometry measurement at 1.00 V during 30 minutes for a solution containing 100 µM fluorescein (top, black labels) and a solution containing 100 µM fluorescein + 1 mM benzocaine (bottom, red labels) in pH 7 buffer. Data points were acquired at t = 0, 5, 10, 15, 20, 25 and 30 minutes. Droplet volume = 50 µL. Experimental details are provided in Supporting Information.

dependent fluorophore, i.e. fluorescein, was added to the solution to monitor the pH real time under a microscope with fluorescence detection. Fluorescein is a well-known fluorophore used as a fluorescent pH indicator, both for in vivo and in vitro applications. It is most useful in the pH-range 5.0-8.5 and reaches its fluorescent intensity maximum at pH > 8.5. It has a λ_{max} of absorption at 492 nm and a λ_{max} of emission at 514 nm.[20] Therefore, the sample was excited at 490 nm and the fluorescence detected. The intensity of the emitted fluorescence of the solution on the SPE surface was monitored real-time during the chronoamperometry measurement and recorded each 5 minutes. The visual evolution of the fluorescence intensity and the mean green light intensity of the image are shown in Figure 8, both for the solution containing solely 100 µM fluorescein (top, black labels) and the solution containing 100 µM fluorescein + 1 mM benzocaine (bottom, red labels).

Figure 8 shows a stable intensity with no significant changes for the solution containing just fluorescein, indicating the pH of the solution remains stable during the experiment. For the solution containing fluorescein and benzocaine, the green light intensity decreases gradually from 177 to 114 on the RGB scale in function of time. This significant decrease in fluorescence intensity indicates a pH-change occurred during the measurement. In accordance to the final intensity of 114, the pH at the end of the measurement should approximately be 6.3, in correspondence to the data gathered in Figure S6. Figure S6 also confirms the fluorescence intensity decreases as the pH is decreases.

A similar chronoamperometry experiment was performed without the fluorophore. Instead, the pH was directly measured using a small pH-electrode prior to and after the chronoamperometry, directly in the droplet on the SPE. The results (section S2.3) show a decrease of the measured pH compared to the starting situation. The results are therefore consistent with these of the fluorescence experiment, providing extra evidence that a local benzocaine-induced pH_S effect is occurring at the SPE surface.

Electrochemical pretreatment aiding cocaine detection in the presence of benzocaine in pH 12 buffer

Although the cocaine SWV signal in the presence of benzocaine is not fully suppressed in pH 12 buffer, the resulting peak potential shift causes an inaccurate cocaine detection in the case the recognition is done based on peak potential. Therefore, a cathodic pretreatment of the electrode surface was proposed as a strategy to assure the accurate SWV detection of cocaine.

Indeed, the electrocatalytic properties of carbon-based electrodes can be improved by activation through electrochemical pretreatment.[6a, 21] Cathodic pretreatment is likely to facilitate or inhibit certain reactions occurring in electrochemical processes.[22] It cleans the surface,[23] creates defect sites through the removal of carbon material, which can be highly reactive,[24] and influences the amount of oxygen-containing functional groups by reducing them.[21c] This seems beneficial towards the electrochemical response of cocaine.[6a] The application of high negative potentials also means dissolved oxygen reduction reactions occur at the electrode surface in aqueous solutions.[25] This reaction consumes protons at the surface and therefore causes the opposite effect of the proposed benzocaine-induced pH_S effect. As a result, cathodic pretreatment aids to minimize the effect of the benzocaine-induced peak potential shift and peak intensity change occurring in the SWV.

The effect of a cathodic surface pretreatment on the cocaine detection in the presence of benzocaine was evaluated by applying various potentials for various times, prior to the SWV scan. The pretreatment potential was varied from -0.4 to -1.2 V, while the time was varied from 5 to 360 s. The pretreatment potential influences the intensity and nature of the pretreatment while a higher pretreatment time allows the pretreatment to be performed more thoroughly.

It was observed that for a pure cocaine solution, the cocaine signal itself tends to shift to different peak potential values after pretreatment, as is depicted in Figure S7 A of the *Supporting Information*. For most pretreatment potentials, the peak potential

tends to drop by 5 - 20 mV during the first 30 seconds of pretreatment, after which the peak potential rises steadily by time to 30 - 40 mV above the initial peak potential value. This should be taken into account for the eventual detection in the binary mixtures of cocaine and benzocaine.

When a conditioning potential is applied for 5, 10 or 30 s, the presence of cocaine cannot be detected in a 1:0.5 mM cocaine:benzocaine mixture while using a pretreatment potential of -0.4 or -0.6 V. Indeed, in those cases the peak shift is still prominent (Figure 2 B). The signal was consequently not attributed to the presence of cocaine. As a quantitative boundary value to account the signal to cocaine, a deviation of ± 40 mV was chosen. If the peak potential of the signal in mixture differs more than 40 mV from the signal of pure cocaine in the same conditions, the signal was not linked to the presence of cocaine. This is shown by the absence of data points in Figure S7 B for 0-30 seconds in the dataset for -0.4 and -0.6 V. From 60 s onwards, the signal is detected within this window and attributed to the presence of cocaine. For a pretreatment potential of -0.8 V, the cocaine signal is attributed from 10 s of pretreatment onwards, and for -1.2 V, 5 s is already sufficient. An increase in peak current for the cocaine signal is also observed with increasing absolute value of pretreatment potential and time (Figure S7 B).

Optimal pretreatment conditions were chosen at -0.8 V as potential and 360 s as time, generally giving stable and intense signals for cocaine in mixture with benzocaine. The results for these optimal conditions are shown in Figure 9 for cocaine (black line), benzocaine (red line) and the binary 1:0.5 mM cocaine:benzocaine mixture (blue line). Only a slight potential shift of 15 mV occurs for the mixture in comparison to the pure cocaine solution, making reliable detection of cocaine possible.

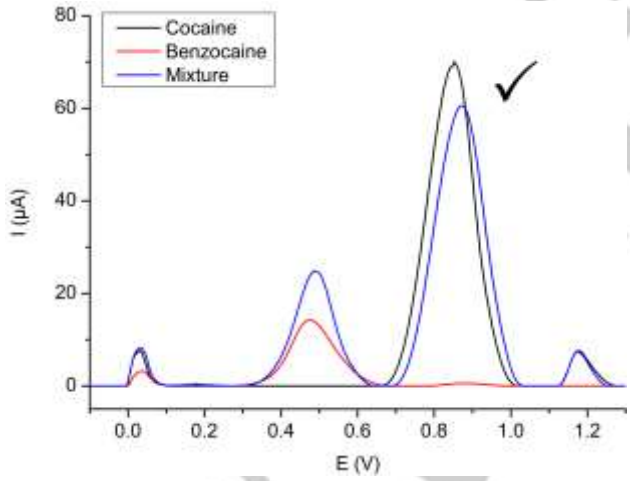

Figure 9. SWVs (pH 12) of cocaine (black line), benzocaine (red line), and a binary mixture (1:0.5 mM) of cocaine and benzocaine (blue line) after a cathodic pretreatment at -0.8 V for 360 s.

Using cathodic pretreatment strategies has provided a solution for the benzocaine-induced interference of cocaine detection in the preferred pH 12 approach. Although the optimized method (concerning analytical performance) was chosen with parameters -0.8 V and 360 s as pretreatment potential and time, respectively, faster and harsher parameters could also be used. Certainly for on-site screening purposes, a fast analysis of cocaine samples is essential. Figure S4 B shows that a combination of parameters -1.2 V and 30 s already provides a solution with sufficient sensitivity (40 µA) and a peak potential shift of just 25 mV compared to pure cocaine in these conditions. Implementing these parameters would raise the total analysis time to approximately 70 seconds, which would make the electrochemical approach very competitive compared to other portable (screening) methods like color tests, infrared and Raman spectroscopy.

Analysis of cocaine in benzocaine-adulterated real samples

To assess the usefulness of the developed strategy for the detection of cocaine in the presence of benzocaine, three benzocaine-containing cocaine street samples were further analyzed with the proposed methodology. Sample 1 contains 33 wt% cocaine, 38.6 wt% benzocaine and 9.0 wt% of lidocaine. Sample 2 contains 66.7 wt% cocaine, 9.5 wt% benzocaine and 19.5 wt% phenacetin. Sample 3 contains 68.7 wt% cocaine and 7.1 wt% benzocaine. Sample 1 is one of the extremes, containing a high quantity of benzocaine. All samples were dissolved in pH 12 buffer to obtain in each case a cocaine concentration of 1 mM. The chosen pretreatment parameters were -1.2 V and 180 s. The results of the subsequent SWV measurement are shown in Figure 10.

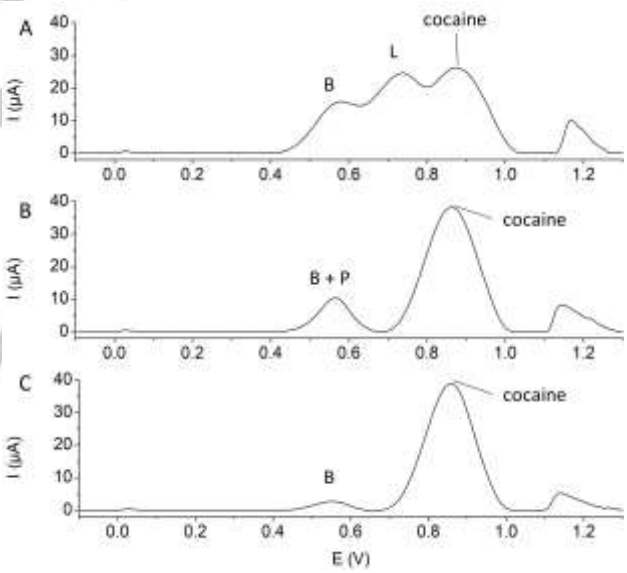

Figure 10. SWVs (pH 12) after cathodic pretreatment (-1.2 V, 180 s) for three benzocaine-adulterated cocaine street samples: (A) sample 1 - 33 wt% cocaine, 38.6 wt% benzocaine and 9.0 wt% lidocaine; (B) sample 2 - 66.7 wt% cocaine, 9.5 wt% benzocaine and 19.5 wt% phenacetin; (C) sample 3 - 68.7 wt% cocaine and 7.1 wt% benzocaine.

The SWVs show the presence of the cocaine signal, as indicated in the figure. Taking into account the information of Figure S7 A, the peak potential of pure cocaine is located at 0.85 V when a pretreatment at -1.2 V is performed for 180 s. The cocaine signal in sample 1 has its maximum located at 0.87 V, sample 2 at 0.86 V and sample 3 at 0.86 V. These are all small deviations from the value for pure cocaine, no greater than 20 mV, which is comfortably inside the earlier proposed quantitative boundary value to assign the signal to cocaine (40 mV). The slightly larger deviation for sample 1 can be explained

by the much larger quantity of benzocaine present in the sample. Next to the cocaine signal, the benzocaine signal was also detected in all three samples (B label) with E_P at approximately 0.56 V. In sample 1, lidocaine is identified as well (L label). Sample 2 contains also phenacetin, but this signal overlaps with the benzocaine signal (B + P label).

The proposed approach shows promising and robust results towards the detection of cocaine in real samples adulterated with benzocaine.

Conclusion

The presence of benzocaine in cocaine powders posed challenges in order to detect cocaine in a reliable manner using voltammetric techniques. In a pH 7 buffer, the SWV signal of cocaine is absent and in a pH 12 buffer, the cocaine signal shifts to higher potentials, along with a peak current drop.

Our findings showed that a local pH_S effect takes place, causing an apparent suppression of the cocaine signal in pH 7 buffers and the signal shift in pH 12. This effect makes the SWV signal of cocaine invisible in the presence of benzocaine as the pH locally drops below pH 6, leading to false negatives. These findings were assembled using voltammetry approaches on mixtures containing different concentration ratios of cocaine and benzocaine and a study of the buffer concentration.

An accurate detection of cocaine in the presence of benzocaine was achieved by performing cathodic pretreatment in pH 12 conditions, avoiding the peak potential to shift and current drop to occur. In succession, this approach was successfully applied in real-sample analysis.

To conclude, the gathered insights concerning the local pH_S interference mechanism are useful to explain unidentified phenomena, involving compounds with properties similar to benzocaine, in voltammetric electroanalysis.

Acknowledgements

The authors acknowledge financial support from IOF-SBO/POC (UAntwerp), the Fund for Scientific Research (FWO) Flanders, Grant 1S 37658 17N and Grant 1SB 8120N, and VLAIO IM [HBC.2019.2181].

Keywords: benzocaine • near-surface pH-effect • potential shift • sensors • voltammetry

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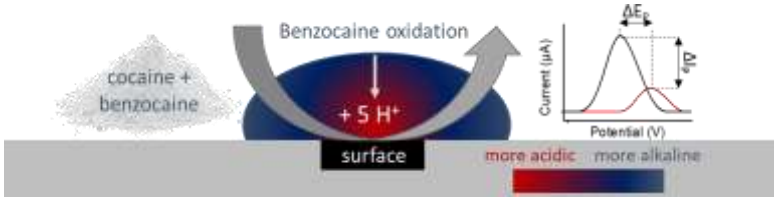

Adulterant interference: Voltammetry interference is often induced by adsorption processes or signal overlap of interferants. We show that less common phenomena could also occur through the examination of benzocaine-adulterated cocaine samples, hampering cocaine detection through a benzocaine-induced near-surface pH-effect, locally acidifying the electrode surface region. A solution is provided through cathodic pretreatment strategies.