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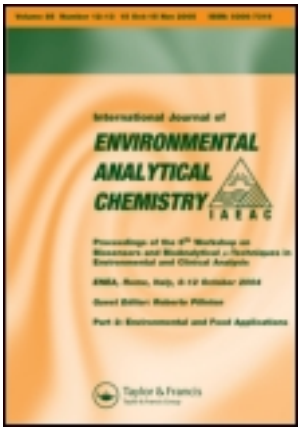

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A method for the analysis of sucralose with electrospray LC/MS in recipient waters and in sewage effluent subjected to tertiary treatment technologies

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A method for the analysis of the artificial sweetener sucralose in sewage water and recipient water was developed. Extraction and clean up was performed with solid-phase extraction utilising Oasis HLB columns. Detection was made by liquid chromatography electrospray mass spectrometry (LC/MS). The triple-quadrupole mass spectrometer was operated in multiple reaction monitoring (MRM) mode. However, 'pseudo MRM' was used, a technique where the two quadrupoles monitor the same m/z. The sodium adduct of sucralose was used for quantification, since lower detection limits were obtained as compared to the sucralose quasi-molecular ion in negative ion mode. The two ions with highest intensity in the chlorine isotope pattern were monitored. The reduction of matrix effects with this approach is discussed. The method limit of quantification (MLOQ) for sewage water was $0.2\,\mu g\,L^{-1}$, whereas for recipient water MLOQ was $0.02\,\mu g\,L^{-1}$. The method was used to analyse effluent samples from an experimental sewage treatment plant (STP) to assess the efficiency of tertiary treatment techniques for removal of sucralose. Filtration through activated carbon was shown to be efficient, while ozonation, advanced oxidation techniques and membrane bioreactors were less efficient. Analyses of receiving waters showed low dilution of sucralose emitted from the STPs.

Keywords: sewage treatment; receiving waters; sodium adduct; matrix effects

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1. Introduction

Sucralose ((2R,3R,4R,5S,6R)-2-[(2R,3S,4S,5S)-2,5-bis(chloromethyl)-3,4-dihydroxy-oxolan-2-yl]oxy-5-chloro-6-(hydroxymethyl)oxane-3,4-diol) has been approved as a food additive by authorities in more than 40 countries [1]. The sweetener has become popular as an additive in low-calorie products such as soft drinks, dairy products and sweets. It is synthesised from sucrose by selective substitution of three hydroxyl groups with chlorine (Figure 1). The chlorination results in high stability of the molecule. Sucralose is not metabolised to energy in the human body and is poorly absorbed [2–3]. This means that a substantial part of sucralose consumed can be expected to end up in wastewater. Although chlorination makes the molecule more lipophilic than the precursor sucrose,

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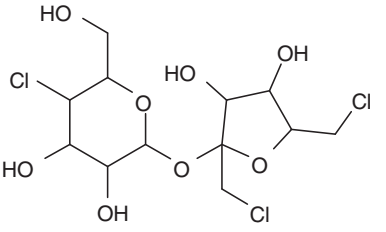

Figure 1. The sucralose molecule.

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it is still hydrophilic (log Kow = 0.3) [2]. It passes unchanged through sewage treatment plants [1]. When released into the environment the molecule is expected to accumulate in the water recipient, since the half life in water is several years [2]. Even though a slow degradation due to hydrolysis of the molecule is expected at low pHs, in nature, where the pH ranges from 4 to 9, hydrolysis is minimal [1]. The potential toxicity of sucralose has been reviewed, and the risk to human health is considered to be low [2]. Ecotoxicological studies, however, have not been performed. Nevertheless, the discovery of sucralose in high ng L^{-1} concentrations in receiving waters has raised concern about this chemical [1].

Modern sewage treatment plants are not adapted for the removal of polar organic compounds, an issue that has been mentioned in several publications concerning pharmaceuticals in the environment [4–6]. Conventional primary and secondary treatment has been proven by others not to remove sucralose [1], but there is no information available on the removal efficiency of tertiary treatment processes.

Analytical methods to quantify sucralose in receiving and STP effluent water are necessary in order to assess the release to and accumulation of sucralose in recipient waters as well as to evaluate the utility of different emission reduction strategies. The sucralose molecule does not contain any chromophores, which results in low sensitivity when using ultra-violet (UV) detection. Only hydroxy-functional groups are present that do not readily protonate or deprotonate, which is unfavourable for detection with LC/MS. Methods for food analysis, with lower demands on sensitivity, have been published that employ LC hyphenated with a refractive index detector, evaporative light scattering detector and electrospray LC/MS [7–10]. Gas chromatography mass spectrometry (GC/MS) has been used for food analysis following derivatisation [11]. However, the analysis of environmental samples usually demands higher specificity and sensitivity. Loos *et al.* [3] used electrospray LC/MSMS in the negative MRM mode for the screening of river surface waters in Europe. This study discusses difficulties with the choice of detection parameters, since the molecule does not readily fragment into detectable ions. Liquid chromatography hyphenated with quadrupole time-of-flight mass spectrometry (LC/QTOF) in the full-scan mode has been used for the quantification of sucralose in lake and sewage water, utilising this technique's ability to perform accurate mass measurements to achieve the necessary specificity [1].

In this study, an alternative and simple approach using LC/MS with a triple-quadrupole instrument for the analysis of environmental samples is presented. Pseudo MRM [12,13], a technique where the two quadrupoles monitor the same m/z and no fragmentation occurs was used. The method was applied to samples of STP effluents from experimental treatment lines at a large STP in Stockholm in order to evaluate the removal efficiency of different tertiary post treatment processes.

The method was also evaluated using samples of receiving waters from the Stockholm area.

2. Experimental

2.1 *Chemicals*

Sucralose (purity 98%) and sucralose-d6 (isotopic purity >98%) were purchased from Toronto Research Chemicals (North York, Canada). Aqueous standards solutions were mixed to appropriate concentrations. The standards were kept at −20°C throughout the study and thawed on a daily basis when needed. Ammonium hydroxide 25% (puriss) was purchased from Fluka (Buchs, Switzerland). Methanol (lichrosolv) was purchased from Merck (Darmstadt, Germany). Water was of milli-Q grade from a milli-Q ultrapure water system, MilliQ PLUS 185 from Millipore (Stockholm, Sweden).

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2.2 *Extraction and clean up*

Two replicates of each sample were analysed. The effluent waters (0.1 L) and recipient water (1 L) were weighed and spiked with 26.5 ng sucralose-d6. Solid-phase extraction (SPE) was used for concentration and clean up. The SPE columns were Oasis HLB 30 μm 60 mg/3 mL from Waters (Milford, USA). The columns were fitted into a vacuum manifold (Supelco Visiprep, Sigma Aldrich Company, Gillingham, UK), and conditioned with 2 mL methanol and 2 mL milli-Q water prior to loading of the sample. Washing was performed with 2 mL 0.5% ammonium hydroxide, and the samples were eluted with 2.5 mL of methanol. The eluate was blown to dryness under a gentle stream of nitrogen (N48 quality, AGA Gas AB, Lidingö, Sweden) at a temperature of approximately 30°C and dissolved in 200 μL methanol : water (1 : 4) before analysis. A blank sample containing pure milli-Q water was treated the same way as the samples.

2.3 *LC/MSMS*

The mass-spectrometric analysis was carried out using a Micromass Quattro II tandem mass spectrometer (Manchester, UK) with an electrospray interface operated in positive ion mode. The capillary voltage was set to 3.5 kV, the cone voltage to 35 V, and the collision energy for the pseudo MRM runs was set to 10 eV. A dwell time of 0.75s was set for sucralose +Na (m/z 419 and 421) and sucralose-d6 +Na (m/z 427) in both SIR (selected ion recording) and pseudo MRM recordings. The acquired masses correspond to the first two peaks in the sucralose adduct isotope cluster and the second peak in the sucralose-d6 adduct isotope cluster (Figure 2). The latter was chosen to avoid interferences from native sucralose, since both molecules contain an isotope with m/z 425. The ion source was set to a temperature of 120°C and the desolvation temperature to 150°C. Nitrogen was used both as the drying gas and nebulising gas at flow rates of 400 L h^{-1} and 20 L h^{-1}, respectively. Argon (N48 quality, AGA Gas AB, Lidingö, Sweden) was used as collision gas at a pressure of 6×10^{-4} mbar during the pseudo MRM runs.

The liquid chromatography pump used was a Waters Alliance 2695 equipped with an auto sampler (Milford, USA). The column was a Hypersil BDS C18 with dimensions 2.1 × 150 mm and 3 μm particle size. The injection volume was 5 μL. The initial composition of the mobile phase was 80% milli-Q water and 20% methanol. This was

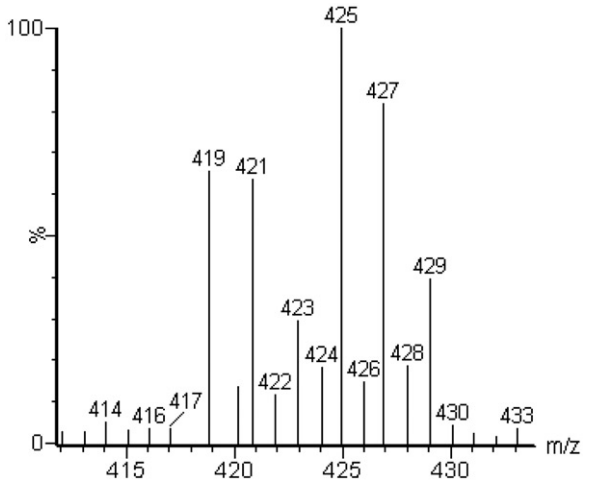

Figure 2. Full-scan spectra of a standard sample containing sucralose and sucralose-d6.

linearly increased to 60% milli-Q water and 40% methanol over seven minutes, followed by an increase of the methanol fraction to 90% for 12 minutes. A pre-column volume of 550 µL was used. MassLynx software was used for controlling system parameters and for acquiring and evaluating data.

2.4 *Sampling*

2.4.1 *Sewage water*

The study was carried out at the Henrikdsal sewage treatment plant (STP, in Stockholm, Sweden), both in the full scale facility and in an experimental pilot plant with parallel treatment lines. A full description of the technical set-up for the six parallel treatment lines is given elsewhere [14].

Incoming sewage was first treated in the full scale STP. The effluent was fed to additional treatment processes in the pilot scale facility. Six parallel treatments were utilised for comparing conventional treatment with the additional treatments (Figure 3). The conventional treatment in the full scale facility consists of chemical precipitation and biological nitrogen removal with a 20 day sludge age. The samples denoted *Hdal out* represent conventional treatment effluent.

The added tertiary treatment processes in pilot scale were as follows:

(1) Activated carbon filtration (*AC*). The filter (Filtrasorb 400) had a 1 h empty bed contact time.
(2) Ozonation at $5\,mg\,L^{-1}$ (O_3 $5\,mg\,L^{-1}$). An Ozone Tech Systems generator (99.5% oxygen from gas cylinder) was used.
(3) Ozonation at $15\,mg\,L^{-1}$ (O_3 $15\,mg\,L^{-1}$).
(4) Ozonation at $5\,mg\,L^{-1}$ plus purification with a moving bed film reactor (O_3 + MBBR). The MBBR (AnoxKaldnes Biofilm-Chip M) had a 2 h empty bed contact time.
(5) Treatment with UV light and hydrogen peroxide (UV/H_2O_2). The UV treatment (Raydar HO-lamp) was $750\,W\,m^{-3}$ and H_2O_2 was added at $10\,mg\,L^{-1}$.

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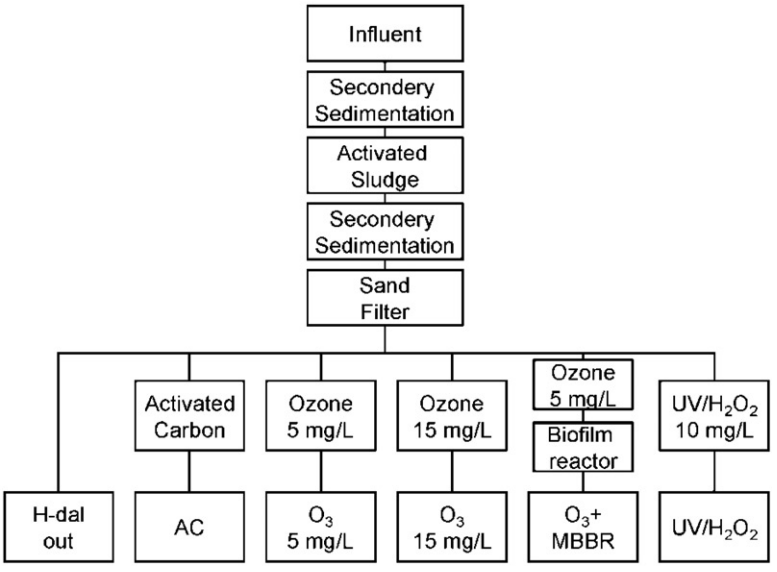

Figure 3. Scheme of the treatment technologies at Henriksdal STP. H-dal out feeds the different post-treatment processes.

The treatment processes had a flow of 100–200 Lh^{-1}. Flow proportional, three-day composite samples were collected during 3–5 March 2008.

2.4.2 *Recipient water*

Surface water was sampled from three STP recipients in the archipelago of Stockholm (Figure 4). Sampling was performed on 7 December 2007. The water was frozen (−20°C) in plastic bottles until analysis. Samples were collected at N 59° 19′06 E 18° 06′12 where the Henriksdal STP (690,000 person equivalents) and Bromma STP (290,000 person equivalents) effluents are emitted. Surface waters were collected in the vicinity of Käppala STP (500,000 person equivalents) at N 59° 21′31 E 18° 14′42 and Tjustvik STP (10,500 person equivalents) at N 59° 17′ 56 E 18° 19′22. The Käppala STP and Bromma STP treatment processes are similar to those in the full scale facility at Henriksdal, although the sludge age and the hydraulic retention time are shorter in Bromma STP. The sewage treatment at Tjustvik STP consists of pre-treatment with screens and grit chambers, followed by chemical precipitation with ferric chloride and biological treatment including nitrogen removal in two batch reactors (SBR) in series. The last treatment is a post-precipitation step with poly-aluminium chloride.

3. Results and discussion

3.1 *Mass spectrometry*

In environmental analysis, complex matrices usually make MRM the technique of choice to get high signal-to-noise ratios as well as high specificity. Even though a considerable amount of time was used to optimise mass-spectrometric settings and mobile-phase

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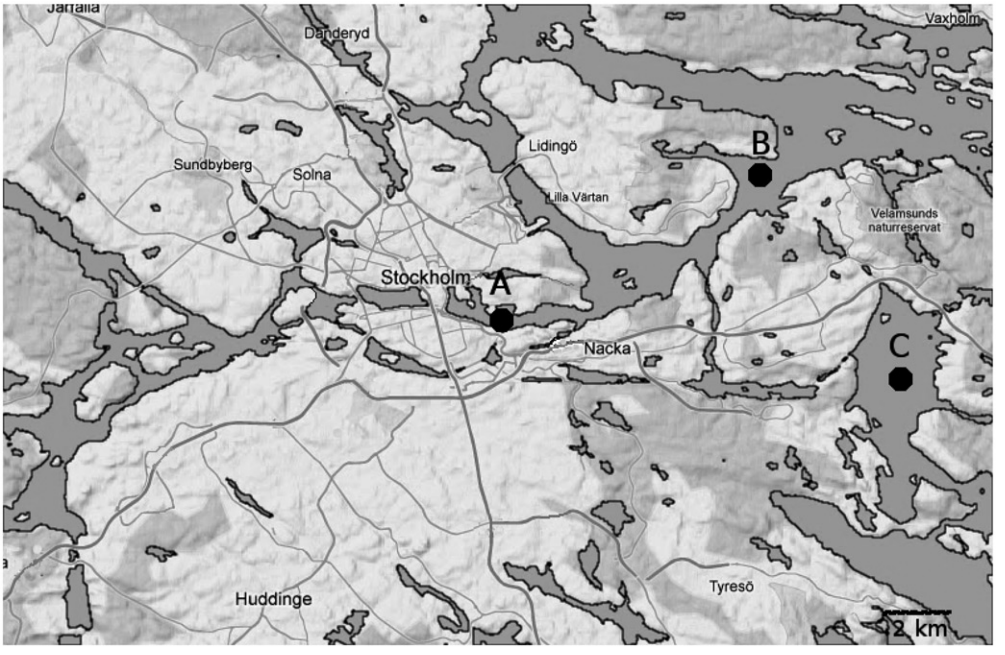

Figure 4. Map of Stockholm showing sampling locations for the receiving water. A: Recipient of Henriksdal and Bromma STP. B: Recipient of Käppala STP. C: Recipient of Tjustvik STP.

composition to achieve fragmentation of sucralose for MRM analyses, fragments with sufficient intensity were not formed. Two other studies [3,10] have analysed sucralose using MRM with the transition of the quasi-molecular parent ion in negative mode fragmented to an ion where one chlorine atom is lost. In both these studies, more modern instruments were used, which may be an explanation why they were successful in developing methods utilising MRM-analysis. One of these studies also discusses problems with low sensitivity, even though they achieved a limit of detection (LOD) of $10\,\mathrm{ng\,L^{-1}}$ applying SPE of 400 mL water [3].

In this work, the following approach was used. Using MRM, the same m/z values were selected in the first and third quadrupoles. This has previously been denoted pseudo MRM [12,13]. This method has been shown to perform better than SIR since collision induced dissociation (CID) in the collision cell fragment co-eluting interferences, and thus reduce matrix effects. Ion suppression, the process by which co-eluting compounds compete for charges in the electro-spray drops, was expected to be the same regardless of whether SIR or pseudo MRM was used. However, extra mass filtering was expected with the use of pseudo MRM, due to dual mass filtering and fragmentation of isobaric interferences in the collision cell. This could provide a higher specificity, in addition to a higher signal-to-noise ratio. In the initial stages of method development, receiving waters were monitored with SIR instead of pseudo MRM. Nevertheless, since two samples of the receiving water showed matrix effects that completely eliminated the signal with the SIR method, whereas the same samples could be quantified with the pseudo MRM method, the latter was more favourable. This indicates that the matrix effects in these samples actually were lowered when utilising the pseudo MRM technique, even though the difference was

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Table 1. Comparison of the concentrations and specificity, including specificity for the standards used to investigate recovery.

Sample	Concentration, $\mu g\,L^{-1}$ ($n=2$)[1] MnRM	Specificity[2] MnRM
Sewage water		
Hdal out	11 ± 3.2	1.1
AC	0.03 ± 0.0	1.4
0_3 5 mg L^{-1}	7.9 ± 1.1	1.0
0_3 15 mg L^{-1}	4.2 ± 0.2	1.0
O_3 + MBBR	6.9 ± 0.8	0.9
UV/H_2O_2	6.6 ± 1.9	0.9
Receiving water		
Käppala	0.41 ± 0.3	1.3
Tjustvik	0.070 ± 0.01	1.2
Henriksdal	0.11 ± 0.04	1.4
Recovery std		
Recovery1		1.0
Recovery2		1.2
Recovery3		1.2

[1]The standard deviation was calculated from the two concentrations (from the two chlorine isotopes) determined for each sample, hence $n=4$.
[2]Ratio between suc-1 and suc-2, average of two replicates.

small, as can be seen in Table 2 (see below). The co-eluting interferences were probably reduced by CID in the collision cell and the double filtering of masses performed by the two quadrupoles. Therefore, the method was developed utilising the pseudo MRM mode.

3.2 *Quality assurance and quality control*

3.2.1 *Specificity*

The chlorine-isotopic pattern for a molecule containing three chlorine atoms, as is the case with sucralose, results in four spectral peaks that differ in mass by 2 Da and occur in the ratio 27 : 27 : 9 : 1. The specific chlorine-isotopic pattern of the sucralose molecule was utilised for the synchronous acquisition of the two spectral peaks with highest intensity denoted suc-1 and suc-2. The area ratio of the two peaks was used to check for peak purity, by comparing the ratio of 1.0–1.4 that was obtained from standards with the corresponding value in the samples. The ratios in the environmental samples, which together with the retention time constituted the criteria for analyte identification, were between 0.9 and 1.4 (Table 1).

3.2.2 *Linearity*

Analysis of six calibration solutions with concentrations from 22 to 992 $\mu g\,L^{-1}$ sucralose containing 100 $\mu g\,L^{-1}$ sucralose-d6 yielded calibration curves with an r^2-value of 0.999.

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3.2.3 *Recovery*

The recovery of the SPE clean-up method ($n = 3$) was measured by using 100 mL water spiked with 25 ng sucralose. Prior to injection these samples were spiked with the same amount of surrogate standard as in the standards. The amount of sucralose recovered was $98 \pm 1\%$.

3.2.4 *Sensitivity*

During development of the method, a higher signal for the sodium adduct in positive mode than for the quasi-molecular ion in negative mode was observed. Therefore, the former was selected for quantitative measurements.

The method limit of quantification (MLOQ) was defined as $5 \times S/N$, from the analysis of a receiving water sample with low concentration. The MLOQ for the sewage-water samples (0.1 L) were $0.2\,\mu g\,L^{-1}$, taken in account that no sucralose was lost during the clean up. The LOQ for the receiving-water samples (1 L) was $0.02\,\mu g\,L^{-1}$.

3.3 *Quantification*

Quantification was performed using sucralose-d6 which was added to the sample as a surrogate standard. To compensate for possible drift, caused by accumulated contamination of parts in the interface, every seventh injection was a quantifier standard containing sucralose-d6 as well as a known amount of native standard. Quantification was performed by comparing the averaged area ratio of sucralose and sucralose-d6 in the quantifier standards bracketing the samples. Comparison of the areas of sucralose and sucralose-d6 in all quantifier standards injected revealed that the matrices in the intervening samples did not cause any drift. The quantified areas were uniform throughout the time needed for running all of the samples. The sample concentrations were calculated as an average between the two replicates where suc-1 and suc-2 were quantified separately, $n = 2$. The standard deviations were calculated from the four peaks that were quantified in the two replicates. The results are shown in Table 1.

3.4 *Matrix effects*

The quantifier standards, which contained the same concentration of sucralose-d6 as the sample extracts, were used for the determination of ion suppression and matrix effects. This was possible since the recovery experiment revealed that very little ($<3\%$) of the sucralose was lost during the clean-up procedure. The area of sucralose-d6 in the quantifier standards was compared with the area of sucralose-d6 in the samples injected nearest to the quantifier samples. In this way ion suppression and matrix effects could be quantified for every sample injected. The formula used for the calculations was:

$$\text{matrix effects} = \left(\frac{\text{area of sucralose-d6 in sample}}{\text{area of sucralose-d6 in quantifier standard}} \times 100\right) - 100 \qquad (1)$$

With this formula enhancement of the signal is presented as a positive figure and suppression as a negative figure. If there is no enhancement or suppression the value is zero. The results are shown in Table 2.

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Table 2. The matrix effects for the samples (both replicates are shown), including matrix effects for receiving waters monitored in SIR-mode.

	Sewage water						Receiving water		
Sample	Hdal out	AC	0_3 5 mg L^{-1}	0_3 15 mg L^{-1}	O_3 + MBBR	UV/ H_2O_2	Käppala	Tjustvik	Henriksdal
MRM	−93, −93	−58, −60	−88, −90	−82, −83	−89, −84	−84, −90	−96, −98	−96, −95	−98, −94
SIR							−97, −100	−95, −97	−97, −100

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Ion suppression was generally high. The receiving waters showed higher matrix effects (−94% to −98%) than sewage water (−58% to −93%). By using the areas of the quantifier standards bracketing the samples any differences of the matrix effects in the interface (i.e. ion suppression) were compensated for.

3.5 *Removal of sucralose in STPs*

The sucralose concentrations in the effluent from the different tertiary treatment steps are given in Table 1. The results show that tertiary treatment of STP effluents with activated carbon can substantially reduce the concentrations of sucralose. An interesting observation is that effluents treated with this technique also showed much less ion suppression (average −59%) in comparison to the other treatments (Table 1). This indicates that substances with the same physico-chemical properties as sucralose are reduced by filtration through active carbon. Having the same retention time, they are competing for charges in the electro-spray droplet. This shows that AC removes also many other interfering matrix compounds.

Tertiary treatment with ozonation, advanced oxidation or MBBR was not as effective in the removal of sucralose. Sucralose was reduced by 60–70% by the highest concentration of ozone used, 15 mg L^{-1}. The low degradability of sucralose is likely attributable to the fact that the oxidants, i.e. molecular ozone and hydroxyl radicals, preferentially react with unsaturated bonds such as in alkenes and aromatic ring structures. Sulphur and nitrogen atoms are also general targets of oxidative attack [15]. None of these functional groups, or elements, are present in the molecule (Figure 1).

High concentrations, in the range of 0.1 μg L^{-1}, of sucralose were measured in the receiving waters. In Henriksdal receiving waters, the dilution was not more than 100 times compared with the effluent. High concentrations of sucralose in receiving waters have been reported previously [1,3]. The recipient water samples stem from bays with limited water exchange and the low dilution probably is a result of this. The high stability of sucralose together with its high water solubility suggests that the molecule may be useful as a tracer for STP effluents in receiving waters and groundwater [16].

3.6 *Concluding remarks*

The pseudo MRM method presented here performed with adequate specificity and sensitivity where conventional MRM could not be used. The comparison of the isotopic area ratio provides sufficient specificity to the analyses.

This study shows that if conventional STPs are to be equipped with an extra treatment step, filtering through activated carbon is effective in the removal of sucralose. The lower matrix effects in those samples compared to effluent from other sewage techniques also indicate that this treatment removes other substances with similar physico-chemical properties.

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