Review article

Application of chromatographic techniques in the analysis of total nitrosamines in water

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ABSTRACT

The use of ozone, chloramine and chlorine dioxide for water treatment results in the formation N-nitrosamines in the treated water. These groups of chemicals and other nitrogen-containing compounds have been described as disinfection by-products (DBPs) which are known for their toxicity. Nitrosamines are a potential source of nitric oxide (NO) which can bind with metals present in the sample matrix leading to formation of metal – nitrosyl complexes and dissolved metals have the potential to increase the total nitrosamines in water. This phenomenon has not received the desired attention and determination of metal-nitrosyl complexes lack standard analytical technique. Chromatography linked to various detectors is the commonest of the techniques for nitrosamine analysis but it is beset with reduced sensitivity as a result of inappropriate choice of the column. Incidentally, chromatographic techniques have not been really adapted for the analysis of metal-nitrosyl complexes. Therefore, there is need for the survey of existing techniques vis-à-vis metal-nitrosamine analysis and to suggest possible areas for method optimization.

1. Introduction

The occurrence of nitrosamines (NAms) as emerging disinfection by-products (EDBPs) in drinking water has been ascribed to the use of chloramine, ozone and chlorine dioxide as chemical oxidants for water treatment [1, 2]. The formation of these contaminants stems from the interaction between the residual disinfectants and the organic matters present in the water [3, 4, 5]. The ubiquity of NAms has received the attention of various authors recently [6, 7, 8]. Jurado-Sánchez et al. [9] reported 18 ng/L of total nitrosamines in drinking water treatment plant in Spain. The presence of these carboxylic acids has also been reported in various water sources from other parts of the world (Table 1).

The volatile (N-nitrosodimethylamine; NDMA, N-nitrosodiethylamine; NDEA and non-volatile, (N-nitrosopropylene; NPRO; N-nitrososarcosine (NSAR) nitrosamines and nitrogen containing disinfection by-products (DBPs) are known to be more toxic than the regulated DBPs [3, 15, 16]. Nitrosamines such as N-nitrosodimethylamine (NDMA) are carcinogenic in rat liver [10, 17]. The presence of nitrosamines in wastewater, source water and drinking water is an emerging issue and of health concern [3, 18]. The United State Environmental Protection Agency (US EPA) added nitrosamines to unregulated organic pollutants and as “probably carcinogenic” (Table 2) [10, 14, 19, 20]. Different permissible levels have emerged for nitrosamines in different countries. For example, 10 ng/L was the maximum permissible limit in California [21] and in Germany. Whereas in Netherland 12 ng/L was the contaminant limits for NDMA in drinking water while Ontario, accepts the maximum limit of 9 ng/L for NDMA [13, 16].

The nitrosyl group present on nitrosamines behave as electron donor (NO⁺), electron acceptor (NO⁻) as well as radical (NO*) resulting into formation of metal complexes.

The reactivity of NO radicals ensures interaction with metals present in the sample forming nitrosamine-metal complex [24, 25, 26, 27]. The analytical significance of this interaction has not been properly investigated. A survey of methodologies available for the analysis of nitrosamines in water shows that the chromatographic techniques are in the forefront of others (Table 3). The widely used method specifically is gas chromatography linked to mass spectrometric detector with carefully selected column.

Till date, there is a paucity of data on metal-nitrosamine complexes concentration in environmental water samples. Therefore, this review...
focuses on the reactions of NO functional group in NAs with certain transition metals and the applications of chromatographic techniques to the analysis of NAs and their metal complexes in the environmental waters.

2. Reactions of nitrosamines with metals

The general, resonance and tautomeric structures of N-nitrosamines are shown in Figures 1, 2, and 3 as to describe their possible reactions. Nitrosamines contain a nitrosyl group (NO) (Figure 1), the nitrogen contains five electrons in the outermost shell (valence electrons); two electrons are used to form double bonds with oxygen while three electrons left behind stay on nitrogen as one and lone pair of electrons [27, 28, 29]. Because of these features NO ligand forms structural bonding and complexes [27, 28].

2.1. Metallic nitrosyl bond (M-NO)

The general, resonance and tautomeric structures of N-nitrosamines are shown in Figures 1, 2, and 3. Also, for better understanding of metal-nitrosyls bond, the molecular orbital (MO) pattern of nitric oxide molecule is presented in Figure 4.

The 6 and 5 electrons in the outermost shell of Oxygen and Nitrogen, respectively are used for bonding. The 11 electrons used in the formation of molecular orbital bond in NO are presented in the following order (Figure 5).

The metallic nitrosyl are as follows [27].

NO gives out an electron for formation of nitrosyl cation and oxygen releases a lone pair electron to nitrogen resulting to bond formation between oxygen and nitrogen (Figure 6).

The unpaired electron (\(\pi^+\)) received by the metal atom (M) changed its oxidation state from 0 to -1 (Figure 7) [27].

The Nitrogen in the NO\(^+\) as electron acceptor leads to formation of pie (\(\pi\)) bond.

Therefore, there is the possibility of NO ligand present in NDMA forming complexes in Figures 14 and 15.

For instance, addition of NO ligand to metals lead to complexes re-action of NDMA with phenylcopper gives NDMA complex (Figure 15) [36, 37].

3. Application of chromatography to the analysis of nitrosamines in environmental waters

Gas chromatography (GC) coupled with various detectors have been employed for the analysis of nitrosamines and other emerging disinfection by-products (EDBPs) (Table 3). These include gas chromatography (GC) with electron capture detector (GC-ECD), nitrogen–phosphorus detector (GC/NPD), thermal energy analyzer (GC/TEA), GC with flame ionization detector (FID), GC coupled with mass spectrometry (GC/MS) [38, 39, 40, 41, 42].

The GC-ECD operates based on the ability of the organic compound to capture a thermal electron and form negatively charged ions. The electron loss is proportional to the quantity of analyte in the sample [43, 44, 45]. It is mostly used for the analysis of nitroaromatic compounds, halogen-containing compounds and conjugated compounds containing weak electrophore groups that can be improved with chemical derivatization [44, 45]. ECD is highly sensitive mostly employed for trace analysis. It has the capability to detect analyte at picogram (10\(^{-12}\)) levels [42, 46, 47, 48]. Similarly, Chienthavorn et al. [41] quantified four nitrosamines (NDEA, NPYR, NPIP, NMOR) with GC-FID. However, GC-ECD and FID have no library data base for the confirmation of the analyte, while GC-MS possesses. In addition, a good precision and linearity have been reported in the analysis of nitrosamines with GC-MS [49, 50, 51, 52, 53].
### Table 3. Chromatographic methods for determination of nitrosamines.

| Matrix                  | Compounds                          | Sample Preparation          | Analytical Instruments                  | Analytical Column               | Detector | LOD (ng/L) | LOQ (ng/L) | RSD (%) | Recovery (%) | Reference |
|-------------------------|------------------------------------|----------------------------|-----------------------------------------|---------------------------------|----------|------------|------------|--------|--------------|----------|
| River Water             | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Rtx 5Sil MS (30 m × 0.25 mm ID × 1 μm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Potable water           | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC EPA Method S21                       | Rtx 5Sil MS (30 m × 0.25 mm ID × 1 μm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Tap & River water       | DMA, EMA, DEA, DPA, TMA, DMTA, DMAPL | No preconcentration steps.   | UPLC (Shimadzu LC-20ADXR)              | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| WTP                     | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE Oasis HLB cartridge/SPE absorbents | HPLC (Agilent 1100)                   | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Drinking Water          | d6-NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Drinking Water          | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Drinking Water          | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Finished/tap/ source water | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Wastewater              | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Drinking/Wastewater     | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Sewage                  | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Bio solid               | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Meat Products (Pork Sausage) | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Deionized Water         | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |
| Cosmetic                | NDMA, NDEA, NMEA, NDPA, NDBA, NDBA | SPE (CCC) Restek (cat. #28032) | GC Agilent 6890 N                       | Phenomenex Spheri C18 (300 μm, 2.5 μm, 5 mm) | Agilent MS 5973 | 2.5–40.6 | 7.9–127.7 | <15    | 72.3–98.6     | [54]     |

N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), N-nitrosopropylamine (NMEA), N-nitrosodiphenylamine (NDPA), N-nitrosodimethylamine (NDBA), N-nitrosodiphenylamine (NDBA), N-nitrosodiethylamine (NDBA).
GC-MS technique explains the abundance of molecular composition and the amount of analyte in the sample in relation to the peak area [45, 64]. Its sensitivity is based on the mass of analyte received at the detector [64, 65]. Because of sensitivity and selectivity, it is used in the selected...
ion monitoring (SIM) mode for the analysis of thermally stable, semi-volatile, less polar and low molecular weight nitrosamines [23, 45, 51, 65, 66]. The study of nitrosamine has been narrowed to the US EPA eight semi-volatile nitrosamine analysis (Method 521) and less attention is given to the non-volatile nitrosamines. The non-volatile NAmS (N-nornicotine, N-piperazine) and labile NDPhA are not amenable to GC-MS methods because they are highly polar and thermally unstable respectively [60, 67, 68, 69]. Also, gas chromatography–tandem mass spectrometry (GC/MS/MS) could gives better sensitivity and selectivity than GC-MS, but cannot be used for the analysis of non-volatile nitrosamines [7, 70, 71]. Analysis of nitrosamines using gas chromatography–low resolution mass spectrometry (GC/LRMS) in electrospray ionization (ESI) mode has also been applied in the analysis of nitrosamines. But its demerit is that it causes chemical interference during low molecular mass nitrosamines analysis [39, 72].

Figure 10. Formation of dative sigma bond.

\[ M \rightarrow NO^+ \]

Figure 11. Movement of π electron for the Formation of π bond.

Figure 12. Formation of π bond.

(LUMO) (π∗ \rightarrow π∗)

Figure 13. The lowest unoccupied molecular orbitals.

\[ \text{MCl}_2 + 2\text{NDMA} \rightarrow \text{MCl}_2(\text{NDMA})_2 \] (nitrosamine-metal complex)

Figure 14. Nitrosamine-metal complex.

Figure 15. Nitrosamine-copper complex formation.

Figure 16. Separation of ten volatile nitrosamines using four different gas chromatographic columns. A, HP-5MS (30 m × 0.25 mm × 0.25 μm) column; B, DB-624 (30 m × 0.25 mm × 1.40 μm) column; C, HP-1701 (30 m × 0.53 mm × 1.0 μm) column; D, HP-INNOWax (30 m × 0.25 mm × 0.25 μm) column (Qiang et al., 2011). It has been published before in Chinese Journal Analytical Chemistry and permission to reproduce the figure has been granted.
3.1. Choice of the columns in the gas chromatographic analysis of nitrosamines

The capacity of gas chromatographic separation column depends on the type of stationary phase and its polarity and the amount of the packing material used (Table 3). This increases the efficiency of the column [49, 58, 73]. A good separation is attained by the distribution of the analytes (solute) on the stationary phase (composition of the adsorbent) and a gas phase that penetrates the stationary phase [74]. Low molecular mass gases are used as mobile phase for the adequate transportation of the solute through the column [74]. A more polar stationary phase retains polar analytes better than less polar solute while a non-polar stationary phase retains any member of homologous series [49, 58]. Different types of column ranging from non-polar (HP-5MS, 5% phenyl-95% dimethylpolysiloxane; DB-5ms 5% Pheny1 95% dimethylpolysiloxane), mid-polar (DB-624, 6% cyanopropyl phenyl-94% dimethylpolysiloxane; DB-1701, 14% cyanopropylphenyl-86% dimethyl polysiloxane) and polar polar column (HP-INNOWax, Polyethylene glycol) have been reported for the analysis of nitrosamines Qiang et al. [49] used column HP-5MS, DB-624, DB-1701 and HP-INNOWax for the analysis of ten nitrosamines and they reported the best peak separation with DB-624 column. The chromatograms reported were shown in Figure 16(A–D) and Figure 17.

In the non-polar column HP-5MS small background level or low signal to noise ratio, better peak resolution(110,386),(197,421) at the beginning and end but poor separation of NDPA, NMOR, NPYR, NPIP at the mid of the chromatogram (Figure 16A). In Figure 16B there was a negligible background noise and all peaks were well separated throughout the chromatogram. High signal to noise ratio at the beginning, analytes were well separated at the end but fairly separated at the mid of the chromatogram (Figure 16C). Figure 16D depicted poor sensitivity and an unreproducible chromatogram could be due to absence of cyanopropyl phenyl and dimethylpolysiloxane.

Similarly, a sharp peak separation with DB-624 column was also reported as shown in Figure 17 [57, 70, 75, 76]. However, there is no published literature on column with 100% dimethylpolysiloxane which could properly yield a better separation.

4. Conclusions

This survey could not find a study specifically dedicated to quantitative determination of metal-complexed nitrosamines. The reason is unknown to us. An overview of the analytical methods has shown that different methods exist for analysis of nitrosamines. However, in our view, the existing reports on total nitrosamine concentration in waters may have therefore been severely underestimated. Gas chromatography with so called mid-polar column made of cyanopropyl phenyl and dimethylpolysiloxane in the ratio 1: 16 (DB-624) and linked mass spectrometer detector is one technique adaptable to the determination of metal-complexed nitrosamines in waters in view of its reproducibility and sensitivity. Attention should focus on the high molecular weight, emerging unregulated and highly toxic nitrosamines as well as metal-nitrosyl complexes occurrence in water. Also, in order to obtain a high quality chromatogram, the chemical composition of the stationary phase used in the column should be improved.

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The authors declare no conflict of interest.

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