The potential of ion mobility spectrometry (IMS) for detection of 2,4,6-trichloroanisole (2,4,6-TCA) in wine

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Abstract

The off-flavor of "tainted wine" is attributed mainly to the presence of 2,4,6-trichloroanisole (2,4,6-TCA) in the wine. In the present study the atmospheric pressure gas-phase ion chemistry, pertaining to ion mobility spectrometry, of 2,4,6-trichloroanisole was investigated. In positive ion mode the dominant species is a monomer ion with a lower intensity dimer species with reduced mobility values (K_0) of 1.58 and 1.20 $cm^2V^{-1}s^{-1}$, respectively. In negative mode the ion with K_0=1.64 $cm^2V^{-1}s^{-1}$ is ascribed to a trichlorophenoxide species while the ions with K_0=1.48 and 1.13 $cm^2V^{-1}s^{-1}$ are attributed to chloride attachment adducts of a TCA monomer and dimer, respectively. The limit of detection of the system for 2,4,6-TCA dissolved in dichloromethane deposited on a filter paper was 2.1 μg and 1.7 ppm in the gas phase. In ethanol and in wine the limit of detection is higher implying that pre-concentration and pre-separation are required before IMS can be used to monitor the level of TCA in wine.

Keywords: 2,4,6-Trichloroanisole, gas phase ion chemistry, ion mobility spectrometry, "tainted wine"

1. Introduction

Trichloroanisole (TCA), particularly the 2,4,6-TCA isomer, is commonly identified as the main compound responsible for the off flavor of wine known as "cork taint", as summarized in some review articles [1-3]. Other isomers of trichloroanisole, substituted tetra- and penta- chloro-anisoles and compounds such as tribromoanisole, 2-methylbornoleol, 4-ethylguaiac, etc., were also associated with off flavor of wine. Furthermore, the use of the common term "cork taint" is misleading as it attributes the origin of the unpleasant aroma of tainted wine to the cork alone, while in fact the odorous compounds may originate from the wood in barrels used for aging wine (especially reusing barrels that have been cleaned), wooden structures within the vineyard and traces of TCA were even detected in water [1-3]. Nevertheless, 2,4,6-TCA originating from the cork material is still considered as the main culprit for tainted wine that affects wine producers globally and the financial losses due to it are estimated in the range of 1-10 billion US dollars annually [2].

One of the first reports attributing the off-flavor of wine to 2,4,6-TCA was published by Buser et al.[4] and the effect of the presence of this compound on the wine flavor has since been confirmed by several investigators [1-3]. The unpleasant odor of tainted wine is readily detected by consumers of wine and is described sometimes as similar to wet cardboard, mushrooms, earthy smell, etc. [5]. The human olfactory threshold for 2,4,6-TCA in wine (in the liquid phase) is usually well below 10 ng L^{-1} and in one study it was estimated to be 2.1 ng L^{-1} and the customer rejection level was only slightly higher at 3.1 ng L^{-1} [6].

Abreviations: TCA – Trichloroanisole; TCP – Trichlorophenol; IMS – Ion mobility spectrometry; SPME – Solid phase microextraction; GC - Gas chromatographic; ECD - Electron capture detector; LOD – Limit of detection; LC-ESI-IMS – Liquid Chromatography electrospray ionization and ion mobility spectrometry; PID -Photo Ionization Detector

50 The origin of these compounds in wine was attributed mainly to the presence of chlorine
51 substituted compounds, including chlorophenol derivatives, in the cork stopper material
52 and sometimes to the content of similar chemicals in wood barrels, especially cleaning
53 materials deployed for re-use of these barrels for aging of the wine [2]. The dominant
54 mechanism for production of 2,4,6-TCA, that is not a naturally occurring compound, is
55 usually described as O-methylation of 2,4,6-trichloro-phenol (2,4,6-TCP) by filamentous
56 fungi [7-8]. TCP and pentachlorophenol are widely used as pesticides in agriculture and
57 other applications including sanitizing wood products.

58 Several analytical approaches been adopted in order to provide an objective measure for
59 the concentration of the compounds responsible for the "tainted" wine flavor [9-19]. The
60 most common methods deploy solid phase microextraction (SPME) fibers to pre-
61 concentrate TCA from the headspace vapor phase or from the wine itself that is generally
62 combined with stir-bar agitation. The pre-concentration step is generally followed by gas
63 chromatographic (GC) separation of the components of the wine or headspace vapors that
64 were adsorbed on the SPME fiber. Finally detection of the GC effluent is carried out by
65 electron capture detectors (ECD) or more commonly by different mass spectrometric
66 instruments that also identify the components. The reported limit of detection (LOD) for
67 2,4,6-TCA by these methods is generally in the 1-100 ng L^{-1} range after pre-
68 concentration.

69 Ion mobility spectrometry (IMS) is a well established method that is frequently used for
70 detection of concealed explosive, contraband drugs and monitoring the presence of toxic
71 chemicals in ambient air [20]. Recently applications in the fields of medical diagnostics
72 and food quality have been developed. Among these are monitoring processes of beer

fermentation [21], determining the spoilage and freshness of muscle food products [22] and detection of molds [23]. These applications take advantage of the fact that IMS has a high sensitivity for compounds with high proton affinity or high electro-negativity values and that the ion chemistry can be controlled to enhance the response to the target analytes while avoiding interferences from many other chemicals that may be present in the matrix. Several chlorophenol derivatives have been studied by liquid chromatography followed by electrospray ionization and ion mobility spectrometry (LC-ESI-IMS) [24]. In a couple of recent publications by Márquez-Sillero et al. 2,46-TCA was determined in water and wine samples by ionic liquid-based single-drop micro-extraction and ion mobility spectrometry [25-26]. The limit of detection that was reported, 0.2 ng L^{-1} [25] or 0.01 ng L^{-1} for a 2 mL wine sample [26], appears to have considerably superseded all other methods.

The objective of the current work was to study the atmospheric pressure gas-phase ion chemistry of 2,4,6-trichloroanisole that pertains to IMS in positive and negative modes and to determine the limit of detection of IMS for 2,4,6-TCA. This is also the first study of the potential of a stand-alone IMS for direct determination of TCA without GC pre-separation or other method for preconcentration. Based on these results we assess the potential for using this technique to monitor off flavor in wine.

2. Materials and methods

2.1 Sample preparation and inlet system

2,4,6-trichloroanisole (TCA) (CAS 87-40-1) was purchased from Aldrich (lot #MKBG3491V) and used without further purification after its purity was tested with GC-

MS (see below). Headspace vapor vials with a volume of 20 mL sealed with 20 mm crimp and 20 mm PTFE/silicone septum3 (all from ChemLab, Barcelona) were used throughout the study. Stock solutions were prepared by weighing samples of TCA and dissolving them in dichloromethane (DCM, CAS 75-09-2, Fluka 66750, 98%) or in ethanol (99.5%, Panreac Sintesis, Barcelona) yielding concentrations of 2.03 and 2.89 μg μL^{-1}, respectively. The DCM stock solution was diluted tenfold to produce a solution with 0.2 μg μL^{-1}.

Duplicate samples of TCA, containing 2 to 40 μg, were prepared by pipetting a known volume of the stock solution, or diluted solution, on a piece (about 5x3 mm) of filter paper (Fisherbrand code 1490) that was placed in a headspace vial. The vial was sealed immediately after the solution was deposited on the filter paper to avoid loss of the solvent and analyte. After at least five minutes at room temperature (about 25ºC) for evaporation and equilibration the vial was inserted into a homemade aluminum heater that was kept at 100ºC for two minutes in order to vaporize the sample. The temperature in the center of the top part of the vial was about 70ºC. At that time two needles pierced the septum: one was connected to a tube that carried a 400 mL min^{-1} stream of purified air, or air seeded with dichloromethane as a dopant, and the other needle was connected through a short piece (about 10 cm) of 1/8" Teflon tubing to the IMS. It was assumed that absorption of TCA vapor on the surface of the tubing would be minimal due to the high flow rate through the narrow tube.

An additional stock solution containing 15 μg μL^{-1} of 2,4,6-TCA in ethanol was also prepared and a 25 μL aliquot (containing 375 μg of TCA) was added to 225 μL of white wine or red wine. A blank sample was prepared by adding 25 μL of pure ethanol to 225

118 μL of wine. Each sample was placed on a 55 mm diameter filter paper and allowed to
119 evaporate to dryness in a hood and then folded and placed in a headspace vapor vial.
120 Analysis of these sealed vials was carried out as described above.

121 In addition, 8.5 mg of 2,4,6-TCA were placed inside a 20 mL headspace vial that was
122 sealed. Taking 2.065 Pa as the vapor pressure of TCA at 25ºC [27], the amount of TCA
123 vapors in 20 mL at equilibrium was calculated as 5.45 μg and this served as means to
124 estimate the sensitivity of the system. Exponential dilution could not be carried out with
125 this system as only a fraction of the 2,4,6-TCA was vaporized.

126 A permeation tube containing 2,4,6-TCA was prepared and placed in a gas generator
127 (Owlstone OVG-4, UK). At a controlled temperature of 100ºC with airflow of 400 mL
128 min^{-1} the concentration of TCA vapors was 1.7 ppm. At lower temperatures the
129 concentration of TCA was below the limit of detection of the instrument.

130 **2.2 The ion mobility spectrometer**

131 The ion mobility spectrometer used in the present study was the handheld Gas Detector
132 Array 2 (GDA2, Airsense Analytics, Germany). In addition to the IMS the GDA2
133 comprises a Photo Ionization Detector (PID), two semiconductor gas sensors (SC) and an
134 electrochemical cell (EC) but in the present study only the IMS was used. The IMS,
135 based on ^{63}Ni ionization, was operated in both positive and negative modes. The
136 instrument was switched on and allowed 30 minutes for stabilization before
137 measurements began. The operating temperature of the drift tube was 44ºC. The sampling
138 airflow was set at 400 mL min^{-1} and the measurements were made with no internal
139 dilution of the sample.

2.3 Signal Processing for the mobility spectra

The signal processing consisted on three main blocks: (i) in the first block spectral preprocessing was carried out, (ii) spectral resolution was performed in the second block and (iii) finally peak intensity calibration and estimation of the limit of detection (LOD) and limit of quantification (LOQ) were processed in the third block. The dataset to perform the tasks was comprised of 8 samples with 0 to 40 μg of TCA deposited on the filter paper and four blank samples measured separately and used uniquely for the purpose of LOD and LOQ estimation. All the spectral signal processing, as well as the estimations of LOD and LOQ was performed using the negative polarity spectra of the IMS.

Pre-processing of the mobility spectra included baseline correction, peak alignment and noise filtering. The baseline from each spectrum was corrected by fitting and subtracting a fourth order polynomial using the first 150 points (from 1 to 5.51 ms) and the last 295 points (from 19.15 to 28.09 ms) of the spectrum where no peaks were identified. Additionally, noise reduction was performed using second order Savitzky-Golay filter [28] with a 15 points sliding window. Finally, the slight misalignment of each spectrum was corrected with shift in x-axis (drift time) taking the position of the reactant ion peaks (RIP) as reference. This pre-processing procedure was applied independently spectrum by spectrum.

Once spectra had been pre-processed, spectral resolution was performed. In order to carry out this task, multivariate curve resolution (MCR-LASSO) [29] was applied to the data matrix yielding a spectral profile and concentration profile. MCR-LASSO is a recent

version of MCR-ALS [30] that uses an instrument model and LASSO regression to improve curve resolution in IMS. The number of pure variables associated with the IMS spectra measurements, was selected by visual inspection of the original spectra. Afterwards, the technique provided the spectral profile of each pure variable and the concentration profiles along the sample transient, for every individual spectrum profile.

Although the use of IMS for quantification purposes is scant, the use of MCR signal processing on IMS spectra has been previously considered [31]. In the present study, a partial least squares model was built based on the concentration profiles obtained from MCR-LASSO. The input pattern for each sample consisted in the concatenation of the concentration profiles for two ionic species related with TCA monomer and dimer ions. The dimension of this vector is 26 (13 spectra x 2 pure components). The final matrix to build the calibration model is 8 samples x 26. PLS model order was decided by a cross-validation procedure (leave one out) optimizing the RMSECV (root mean square error in cross validation).

Once the model had been built, four blank samples, which were measured separately, were projected over the calibration model, and their predicted value was used to estimate LOD and LOQ. The limit of detection and limit of quantification determination was carried out in accordance with IUPAC [32]:

$$LOD = \bar{y} + K_D\sigma$$

$$K_D = t(v,\alpha)(1+1/nb)^{1/2}$$

$$LOQ = \bar{y} + K_Q\sigma$$

183 $$K_Q = 3K_D$$

184 Where $\bar{y}$ is the mean predicted value for the blanks, σ is the corresponding standard
185 deviation, *t(v,α)* is the *t*-student distribution value of v degrees of freedom and confidence
186 level α and *nb* is the number of blanks.

187 **2.4 GC-MS measurements**

188 The purity of the 2,4,6-TCA was determined from GC/MS (Focus GC with DSQ II mass
189 spectrometer, Thermo Scientific) measurements of the headspace vapor emanating from a
190 sample of 47 mg that was placed in a 20 mL vial that was hermetically sealed with a
191 PTFE/silicone septum. The sample was thermostatted for 10 min at 100ºC under constant
192 stirring. Afterwards, 1 mL of the headspace vapors was introduced into the injector port
193 of the gas chromatograph. Chromatographic injection was made in split mode (1:50) at
194 250ºC. A TRB-5MS chromatographic column (30m x 0.25mm i.d., 0.25µm film
195 thickness) was used with an oven temperature program of 60ºC (2 min) at 20ºC min^{-1} up
196 to 260ºC (2 min). The carrier gas was high-purity helium with a flow-rate of 1.0 mL min^{-1}
197 . Mass spectra were recorded by electron impact (EI) ionization at 70eV and ion source
198 temperature of 200ºC.

199 **3. Results and discussion**

200 **3.1 Sample purity**

201 A single peak appeared in the gas chromatogram with a retention time of 8.32 min
202 (Figure 1a). The mass spectrum corresponding to this peak is shown in Figure 1b that
203 displays the mass spectrum of 2,4,6-TCA obtained in full scan mode (mass range 35-350

Da). Identification of TCA was confirmed through the comparison of the NIST-library mass spectrum of TCA (Figure 1c) with the mass spectrum obtained from the sample. The ions around m/z 210 are attributed to the quasimolecular ion with typical isotopic pattern of three chlorine atoms, while the ions around m/z 195 represent the same pattern after the loss of the methyl group.

[Figure 1a, 1b, 1c, about here]

3.2 Reduced mobility values of 2,4,6-Trichloroanisole in positive and negative mode

The ion mobility spectra from the headspace vapor of 2,4,6-trichloroanisole in positive and negative modes in purified air are shown in Figure 2a and 2b, respectively, and the spectra with vapors of dichloromethane as a dopant are depicted in Figure 3a and 3b, respectively. Two peaks with reduced mobility values of 1.58 and 1.20 $cm^2V^{-1}s^{-1}$ were observed in the positive ion spectra. As an IMS-MS instrument was not available identification of the ions and peak assignment was based on ion chemistry and drift time considerations. Thus, these peaks were assumed to arise from a TCA monomer and dimer ions, respectively, as ethers in general are known to form protonated monomers and dimers [33].

The dominant ion in the negative mobility spectrum was an ion with a reduced mobility value of 2.69 $cm^2V^{-1}s^{-1}$, identified as the chloride ion that is commonly detected in many aliphatic and aromatic chlorine compounds [20]. The ion with a reduced mobility of 1.64 $cm^2V^{-1}s^{-1}$, is quite similar to the ions reported for 2,4,6-, 2,4,5- and 2,3,5- isomers of trichlorophenol with mobility values of 1.617, 1.622 and 1.628 $cm^2V^{-1}s^{-1}$, respectively, measured at a drift tube temperature of 216ºC [24]. These were identified as analogous to

226 the pheoxide ion observed in phenol, i. e. in the present work the peak at 1.64 $cm^2V^{-1}s^{-1}$
227 was assigned to trichlorophenoxide ($C_6H_2Cl_3O^-$) probably formed by loss of the methyl
228 group. Other peaks in the negative ion mobility spectra were observed with reduced
229 mobility values of 1.48 $cm^2V^{-1}s^{-1}$ and 1.13 $cm^2V^{-1}s^{-1}$. The former was assumed to be an
230 adduct between a TCA molecule and a chloride ion and the latter a chloride bridged
231 dimer ion. These assignments are based on the fact that aromatic compounds in general,
232 like molecules of aromatic explosives, tend to form such adducts with negative ions
233 under conditions that prevail in the IMS drift tube [34]. These assignments are supported
234 by the fact that when dichloromethane is used as a dopant the intensity of the peak at 1.48
235 $cm^2V^{-1}s^{-1}$ assigned to the chloride adduct increases relative to the peak at 1.64 $cm^2V^{-1}s^{-1}$
236 that was attributed to the phenoxide species.

237 [Figure 2 and 3 about here]

238 **3.3 Relative Sensitivity for TCA dissolved in dichloromethane, ethanol and wine**

239 The relative sensitivity of the detection system for 2,4,6-TCA dissolved in dichloro-
240 methane, ethanol and wine can be assessed from measurements of TCA deposited on
241 filter paper in a headspace vial. The relative signal intensities in positive and negative
242 mode are summarized in Table 1, and evidently the sensitivity decreases in the order
243 DCM>Ethanol>wine. The relatively low sensitivity for TCA in wine could be in part due
244 to the long time allowed for drying of the sample that could have also resulted in loss of
245 some of the TCA in the spike. It should be noted that several new peaks appear in the
246 positive and negative mobility spectra of the blanks and spiked wine samples.

247 The relative recovery efficiency can be derived from these measurements. Thus, if we
248 assume that the recovery of TCA from dichloromethane solution is unity then recovery
249 from ethanol solution, white wine and red wine would be 56%, 7% and 9%, respectively,
250 on average for the three main ion species.

251 The dichloromethane dopant increased the sensitivity of the system in negative mode and
252 hardly affected the signal intensity in positive mode. In the present system the sensitivity
253 is practically doubled with the addition of the dopant, which is reflected in the intensity
254 of the signals of the ions at 1.48 and 1.13 $cm^2V^{-1}s^{-1}$.

255 [Table 1 about here]

256 **3.4 Calibration of the IMS system for 2,4,6-TCA and the limit of detection**

257 A calibration curve was prepared for 2,4,6-TCA dissolved in dichloromethane and
258 deposited on a piece of filter paper placed in a headspace vial that was sealed and heated
259 before measurement. The spectra were processed according to the procedure described
260 above in improve the quality of the quantitative information.

261 Figure 4a depicts the pure negative mode ion mobility spectra of TCA obtained by MCR-
262 LASSO and shows that the method has perfectly identified the presence of two main
263 peaks in the selected drift time range of interest. They are the pure spectra profiles of the
264 TCA monomer and dimer ions. As the headspace vapor is carried from the vial to the
265 IMS the concentration first increases, reaches a maximum after 5 to 9 seconds and then
266 decreases as the vapor is diluted by the carrier stream. These concentration profiles of
267 the TCA monomer ion (Ko=1.48 $cm^2V^{-1}s^{-1}$) are presented in Figure 4b for samples
268 containing 0-40 μg of TCA.

[Figure 4a and 4b about here]

"Leave one out" cross-validation procedure indicated that the optimum latent variable was five. A plot of the predicted concentrations against the real values can be observed in Figure 5. The root mean square error in cross-validation was 1.4 μg, and the R^2 was 0.99.

[Figure 5 about here]

The limit of quantification was 4.3μg and the limit of detection was found to be 1.7 μg of 2,4,6-TCA deposited from a dichloromethane solution on a piece of filter paper placed in a headspace vial.

4. Conclusions

This work presents a discussion of the gas phase ion chemistry pertaining to ion mobility spectrometry measurements of 2,4,6-trichloroanisole in positive and negative modes. Even without definitive identification based on IMS-MS measurements the ions observed in the positive and negative ion mobility spectra can be assigned consistently according to sound arguments based on gas-phase ion chemistry and mass-mobility considerations. In positive mode two ionic species were attributed to the protonated monomer and dimer, and in negative mode a trichlorophenoxide ion as well as a monomer and dimer formed through chloride ion attachment were observed. The reduced mobility values of these ions in air at 44ºC are reported here for the first time. The experimental set up can perhaps be improved by heating the tubing between the sample vial and the IMS inlet port, although there was no evidence that absorption of TCA vapor on the tubing played a role.

290 Calibration curves were prepared and the limit of detection of the system was determined
291 to be 1.7 μg for a sample dissolved in dichloromethane and deposited on filter paper. This
292 limit of detection is inferior by several orders of magnitude to the limit of detection
293 reported recently [25,26]. However, a close examination of the mobility spectra displayed
294 in those reports shows that the calculation of the LOD was based on preconcentration and
295 pre-separation of the TCA and on measurement of the chloride ion while in the present
296 work an ion species that arises specifically from the 2,4,6-TCA analyte was used for the
297 LOD calculation and the IMS was operated as a stand-alone device.

298 Determination of 2,4,6-trichloroanisole in wine requires pre-concentration (enrichment)
299 and pre-separation and a sensitive analytical device for measuring the signal intensity.
300 The present work did not address the techniques for pre-treatment of wine samples and
301 focused on the potential for using ion mobility spectrometry as the measurement device.
302 The limit of detection found here would require a substantial enrichment factor,
303 especially considering that the "off flavor" attributed to TCA is apparent at levels below
304 10 ng L^{-1}.

305

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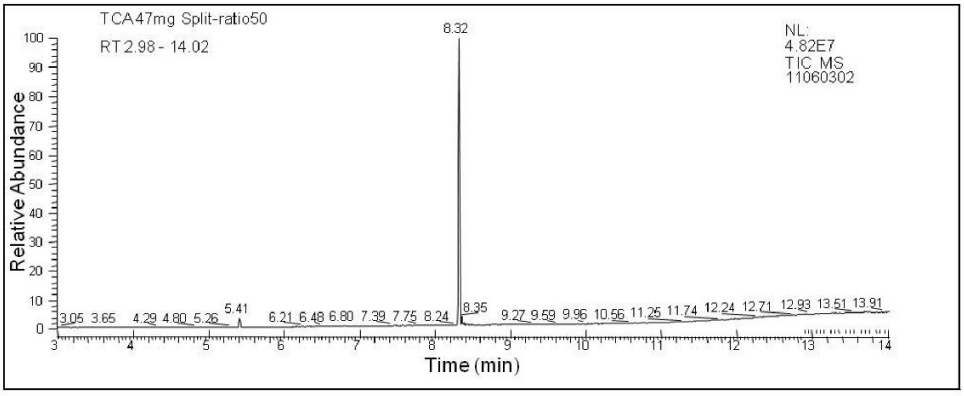
374 **List of Figures:**

386

387 Figure 1a



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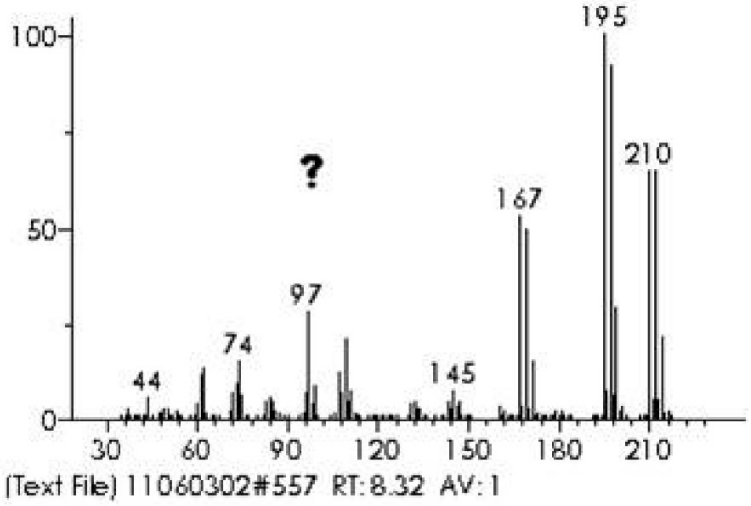
389

390 Figure 1b



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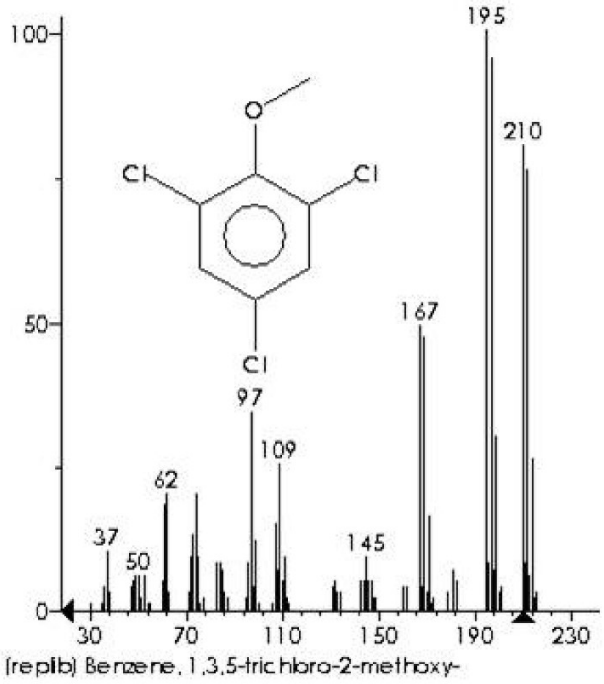
393 Figure 1c



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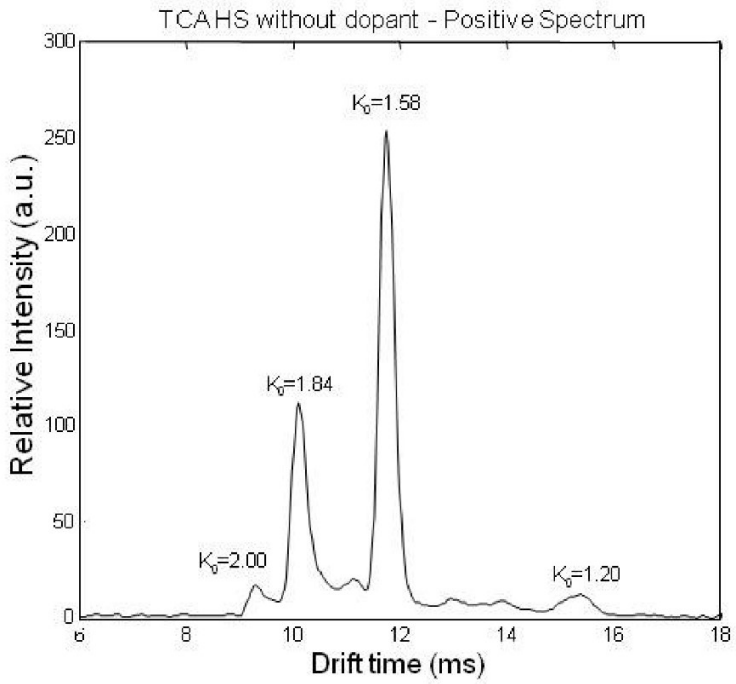
396 Figure 2a



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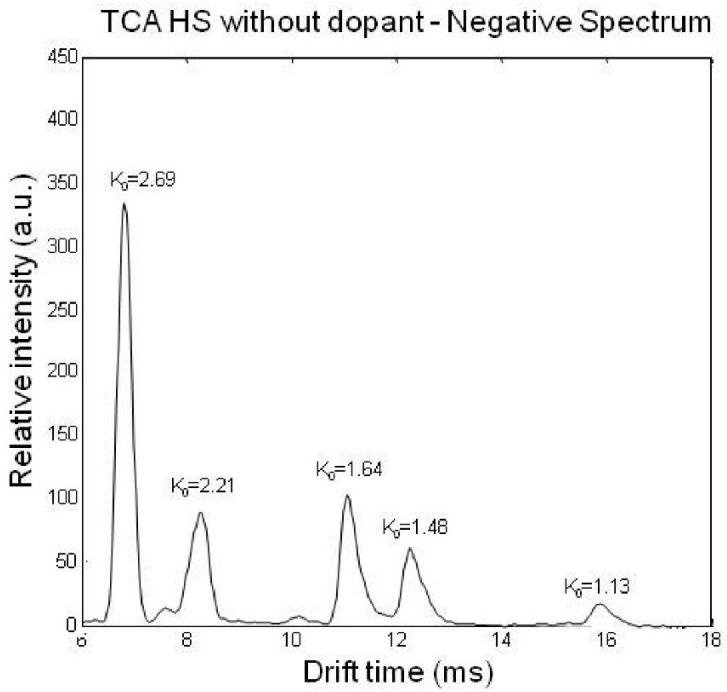
399 Figure 2b



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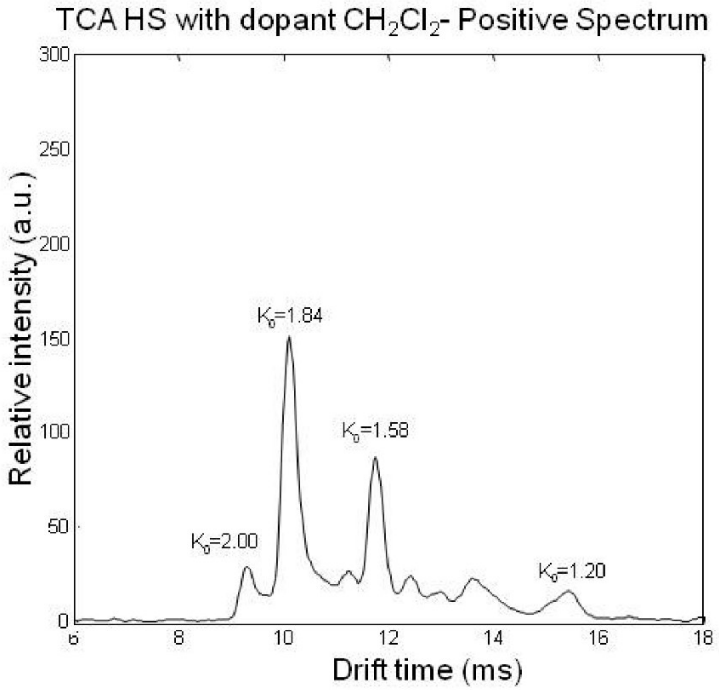
402 Figure 3a



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405 Figure 3b

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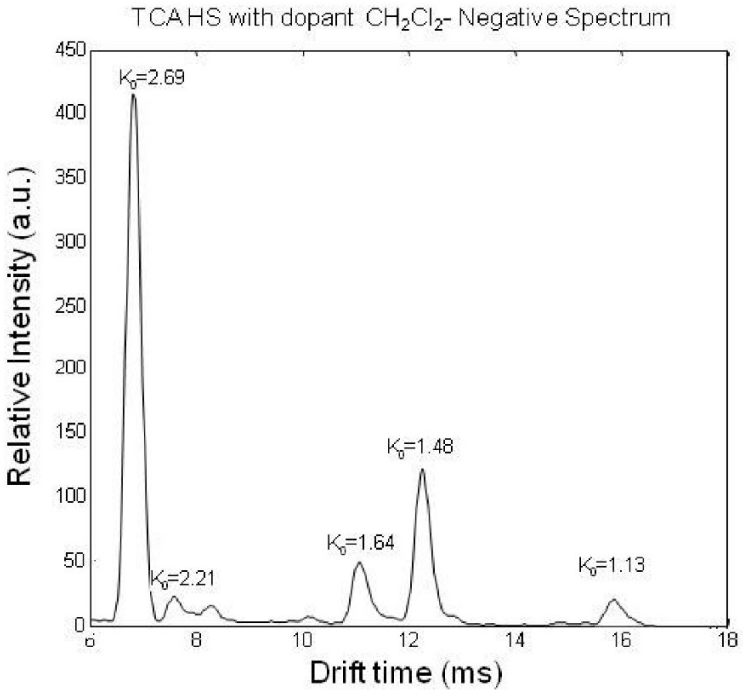

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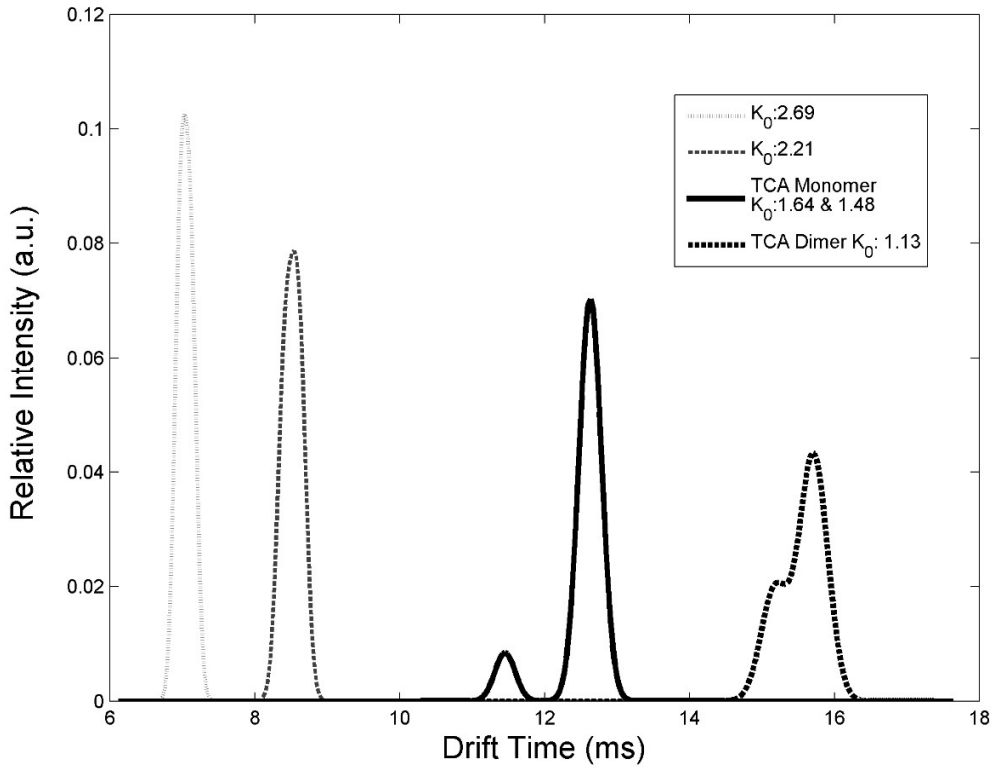
409 Figure 4a



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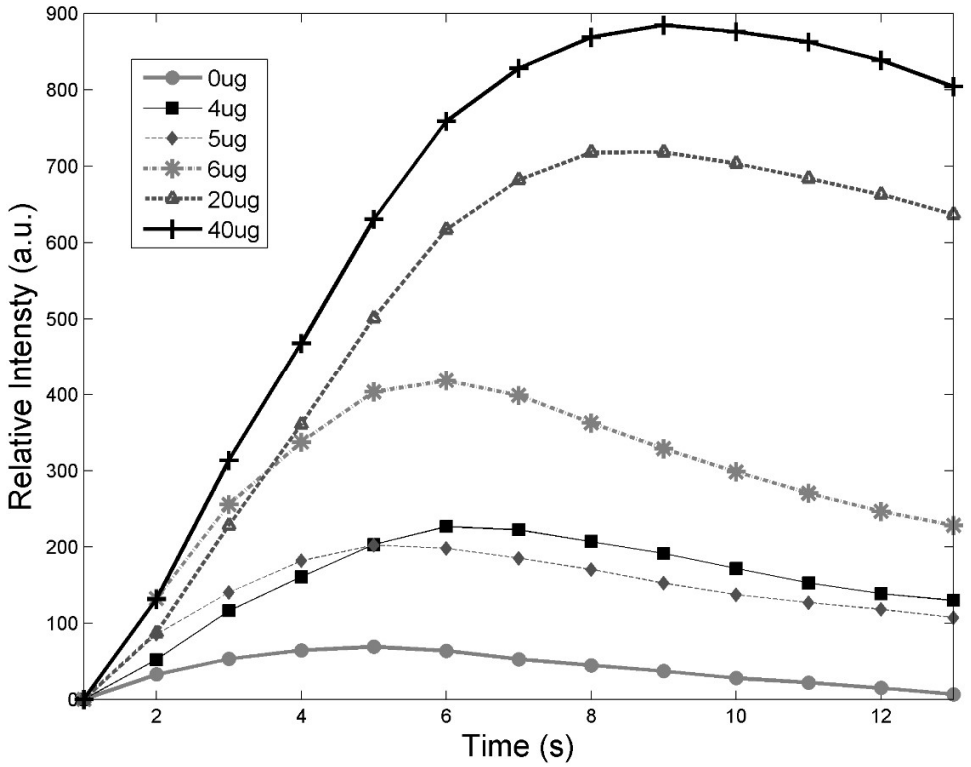
412 Figure 4b



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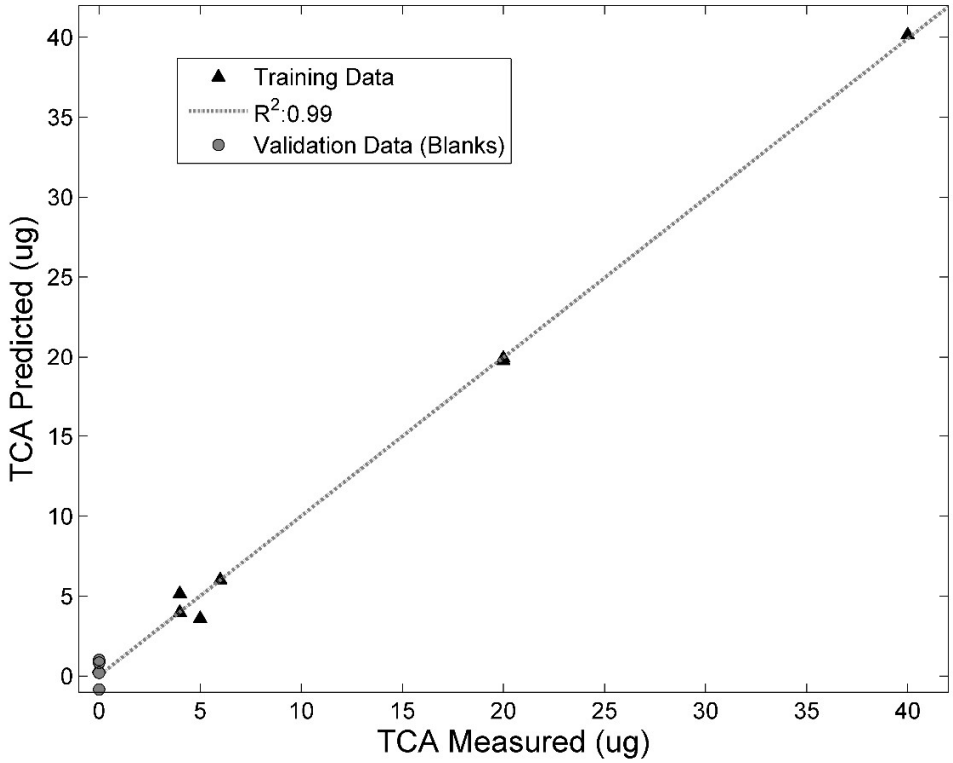
415 Figure 5



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418 **Table 1**. The relative sensitivity [µV/µg] of the GDA2 to 2,4,6-trichloroanisole dissolved
419 in dichloromethane, ethanol and wine and deposited on filter paper in a heated headspace
420 vial. The recovery efficiency relative to TCA in dichloromethane solution is shown in
421 parenthesis.

Sensitivity [µV/µg]	Positive spectra at K_0=1.58	Negative spectra at K_0=1.64	Negative spectra at K_0=1.48
Red wine spiked with 375 µg TCA	45 (8%)	95 (13%)	47 (5.6%)
White wine spiked with 375µg TCA	44 (8%)	28 (4%)	77 (9%)
58 µg TCA in Ethanol	450 (78%)	470 (65%)	200 (24%)
60 µg TCA in CH_2Cl_2	580	720	840

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