

The Analgesic Metamizol (Dipyrone). Part 2: Adsorption, Oxidative and Reductive Degradation

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Abstract A drastic increase in pharmaceuticals consumption has resulted in a high load of pharmaceuticals in wastewater, resulting in an obvious need for detoxification. Metamizol is a typical representative of an analgesic non-steroidal agent that hydrolyzes into 4-Methylantipyrine (4-MAA). In this article, we show some simple adsorption, oxidation and reduction experiments that can either collect or degrade 4-MAA and some of its related metabolism products. The main successful method in detoxifying these substances is shown to be reduction at moderate temperature.

Keywords: metamizol (dipyrone), adsorption, oxidative and reductive degradation

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1. Introduction

Metamizol (dipyrone or Novalgin®) is a pharmaceutical that is widely used as an analgesic and antipyretic in various countries in Europe, Africa and South America, although it has been banned in North America and some European countries because of its collateral effects [1,2,3]. Oxidative processes are widely used for removing pharmaceutical products from wastewater. These processes use the *in situ* formation of OH· radicals which cause unselective degradation of different organic molecules. These radicals are formed as a result of several processes: Fenton and photo-Fenton processes are based on the redox reaction between Fe²⁺ and H₂O₂ with and without irradiation with UV light. UV-irradiated TiO₂ in aqueous solvents is not only used to generate OH· radicals; it can also create electron-hole pairs (excitons) which can oxidize organic molecules [4]. The latter photocatalysis process can be induced by solar irradiation and can work at ambient temperatures.

Giri and Golder [4] describe the mechanism of OH· radical formation and identify more than twenty oxidation products of 4-Methylaminoantipyrine (4-MAA), the hydrolysing product of metamizol. Investigations into different oxidizing agents have shown that photo-Fenton is the main effective oxidation process: around 90% of 4-MAA is oxidized after 20 minutes, and the total organic carbon (TOC) removal is about 60%.

Some work has been done to either electrochemically generate H₂O₂ [5,6] or to degrade metamizol using supported electrodes [7,8,9,10]. Reis et al. [7] used anodes comprising boron-doped diamond films supported on titanium in a flow-by reactor. Spectroscopic and chromatographic

analysis revealed that metamizol was degraded completely within 120 min. The resulting products, however, were not identified. Assumpcao et al. [8] used a cerium nanostructured carbon diffusion electrode to generate an electro-Fenton reaction. H₂O₂ was generated through oxygen reduction. The incorporation of cerium into the electrode enhances metamizol degradation (57% mineralization at -1.1 V). Celli et al. [9] used the oxidation of Ag to Ag₂O to decrease the band gap of wurtzite ZnO from 3.13 eV to 2.85 eV. The resulting Ag₂O was used to oxidize ascorbic acid to dehydroascorbic acid to form Ag. This chemical system was then irradiated at 525 nm, and about 80% of metamizol was removed through the formation of O₂· as a result of the interaction between O₂ with the electrons of the conduction band of ZnO/Ag. Da Silva et al. [10] treated 4-MAA in acidic solution with electrogenerated H₂O₂ at boron-doped diamond. The authors optimized current density, pH and the concentration of 4-MAA. With those optimized values, 99% of 4-MAA was removed after 7 min. The products were toxicity tested using *Artemia salina* larvae.

Some features of the mass-spectrometric and electrochemical analysis of metamizol and some of its metabolized products have been presented in the first part of our study in *World J. Chem. Educ.* [11].

In this article, we concentrate on the adsorption of 4-MAA and byproducts, oxidation with TiO₂ and ozone, electrolysis and reductive gas phase degradation.

2. Pedagogical Objectives

Education for sustainable development is not limited to methods or models to reduce climate change; it also deals with introducing waste into water, air and soil. Chemical

degradation of pharmaceuticals is a major challenge for chemical analysts and engineers. In an educational sense, students must be sensitized to the consequences of introducing pharmaceuticals into the environment. This article contributes to chemical methods that could reduce the environmental risk caused by one of the most widely used pharmaceuticals, metamizol.

3. Experimental

Chemicals and Materials

Adsorption: Activated carbon (Roth, Germany), magnetic stirrer, beaker

Ozonisation: Ozoniser (Fischer, Germany). Oxygen to ozone conversion rate: 30%.

Oxidation with TiO_2 : Mercury-medium pressure lamp (Hönle, Germany), TiO_2 (Degussa, Germany).

Electrolysis: Platinum grid electrodes (5 cm * 5 cm), NaH_2PO_4 as conduction salt.

Gasphase degradation: Carbolite tubular furnace (HST 12-40, Carbolite Gero), Perfusor VI (B. Brand), 10 mL syringe, zero valent iron (Merck), freezing mixture (ice / sodium chloride).

Analysis:

GC-MS: GC: Hewlett-Packard 6890 with an HP-5 column. Temperature profile: starting temperature, 100°C, 2 min isotherm temperature ramp, 15°C/min; end temperature, 270°C, 2 min isotherm. MS: Hewlett-Packard 5973; injection: 1 μ L.

Cyclic voltammetry: Potentiostat (μ Stat 400, DropSens), screen-printed electrodes (SPEs) (DRP-220 Au-AT, Au as the working electrode, Au as the counter electrode, Ag as the pseudo-reference electrode).

4. Results

4.1. Adsorption with Activated Carbon

An aliquot mixture of 4-MAA, aminoantipyrine (AA) and dimethylaminoantipyrine (DMAA) (1 mmol in 10 mL methanol, respectively) was mixed with different masses of activated carbon (0 g, 1 g, 2 g) in a beaker. The mixture was stirred for about 30 min. The adsorption temperature was 20°C. 1 μ L of the supernatant was directly injected into the GCMS. The residue was extracted five times with methanol in a Soxhlet apparatus. The extract was concentrated in a rotary evaporator to dryness and 1 mL methanol was added and analysed in the GCMS. A recovery rate of 4-MAA, AA and DMAA of nearly 100% was found.

Figure 1 shows the results. The adsorption rate was about 36% (1 g) and 55% (2 g).

4.2. Oxidation

4.2.1. TiO_2

1 g of TiO_2 was mixed with 4-MAA, AA and DMAA. The mixture was irradiated with a mercury UV lamp at different wavelengths (254 nm and 366 nm) for 4 h each. Figure 2 shows the principle mechanism of the electron-hole separation in TiO_2 , i.e., the formation of excitones.

The results in Figure 3 reflect those of Giri and Golder [4], who showed that the removal of 4-MAA has two distinct rate periods: the initial faster removal followed by a constant rate, even with a notable amount of unreacted 4-MAA. In our own experiments, only 60% of the mixture of 4-MAA, AA and DMAA reacted (Figure 3).

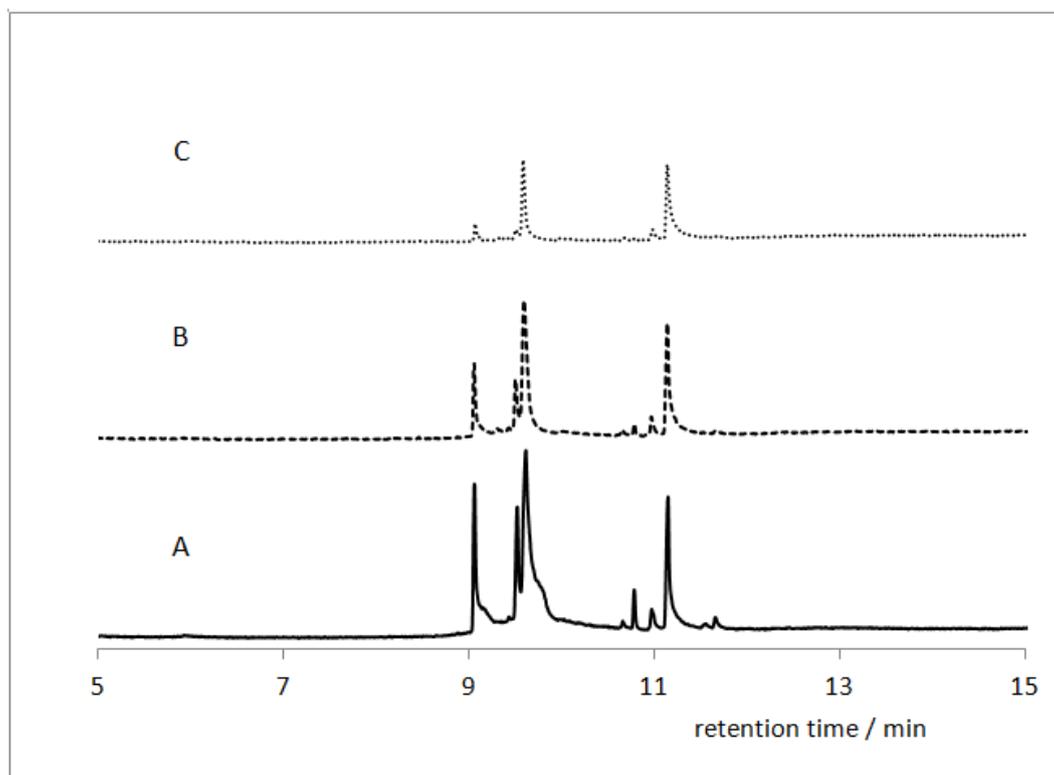


Figure 1. A: 0g, B: 1 g, C: 2g activated carbon

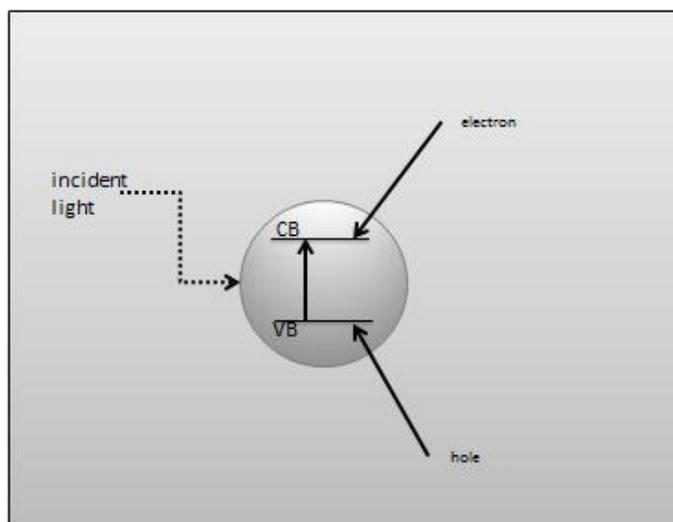


Figure 2. Scheme of the formation of excitones in TiO_2 : The incident light (254 nm and 366 nm) produces holes in the valence bond (VB) and electrons in the conducting band (CB). The bandgap of the employed TiO_2 modification anatase is about 3.23 eV (= 385 nm)

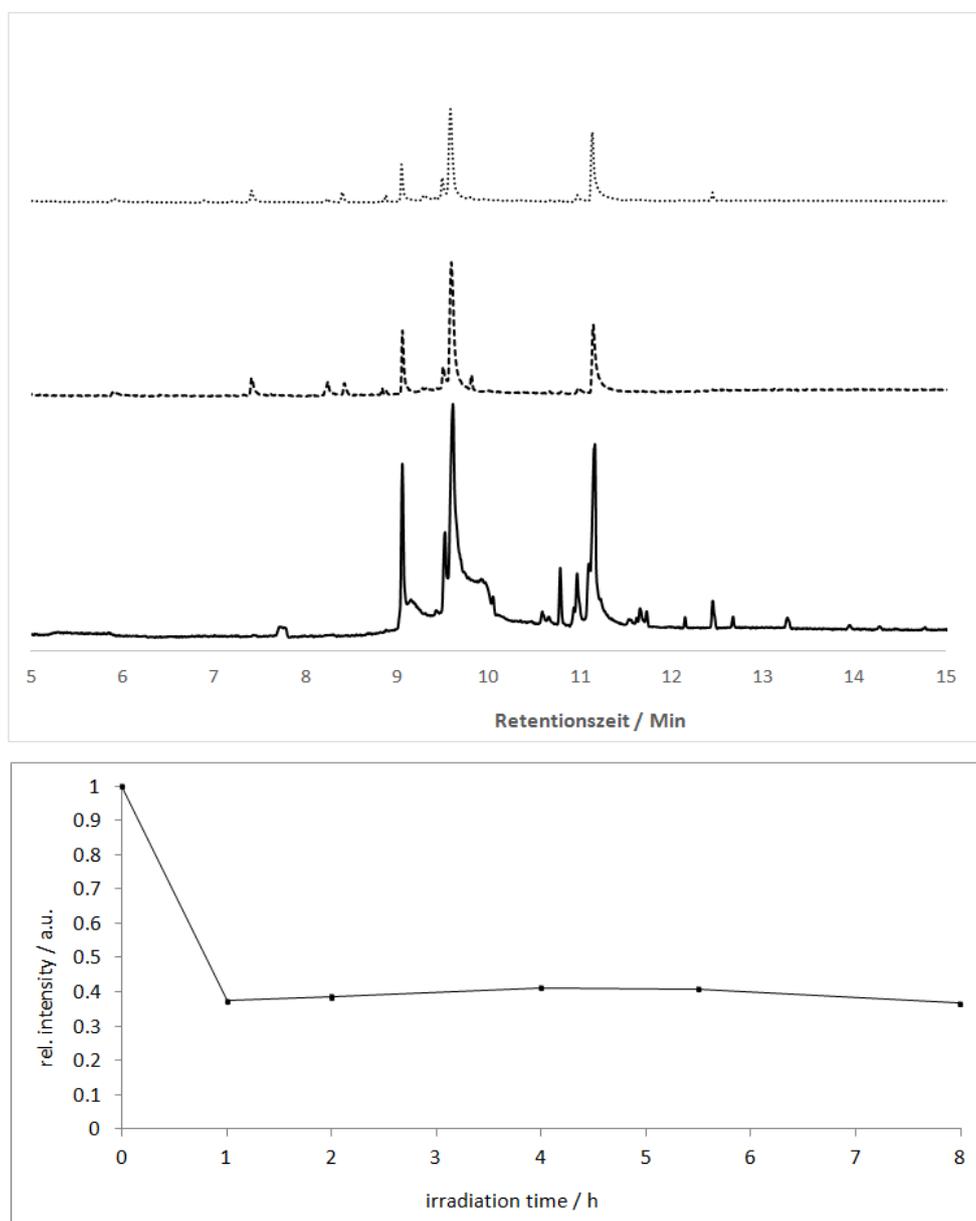


Figure 3. Top: GCMS of the products of reduction of 4-MAA, MAA and DMAA with 1g TiO_2 without irradiation (bottom), at 366 nm (middle) and at 254 nm irradiation wavelength (top). Irradiation time: 4 h. Bottom: Degradation rate with 1g TiO_2 at different irradiation times (366 nm).

Increasing the amount of TiO_2 does not influence the degradation rate, perhaps because this causes agglomeration and hinders light penetration. Perez-Estrada *et al.* [12] found that the peaks at retention times lower than 9 min result in opening the pyrazolinone ring.

4.2.2. Ozone

Ozone from an ozoniser was bubbled into a methanol solution of 4-MAA, AA and DMAA. Oxygen alone does not oxidise these substances, as was proved in an earlier experiment.

Perez-Estrada *et al.* [12] identified the degradation products by GCMS and LCMS and estimated that the

peaks at retention times lower than 9 min are the same products as those in 4.2.1.

4.3. Electrolysis

Figure 5 shows the cyclic voltammogram of an aqueous solution of metamizol with NaH_2PO_4 as conduction salt with and without electrolysis. The two current peaks at 0.5 V and 0.6 V have already disappeared after 100 min of electrolysis. After 600 min, the current peak at 0.95 V decreases gradually with electrolysis time (see the arrow in Figure 5).

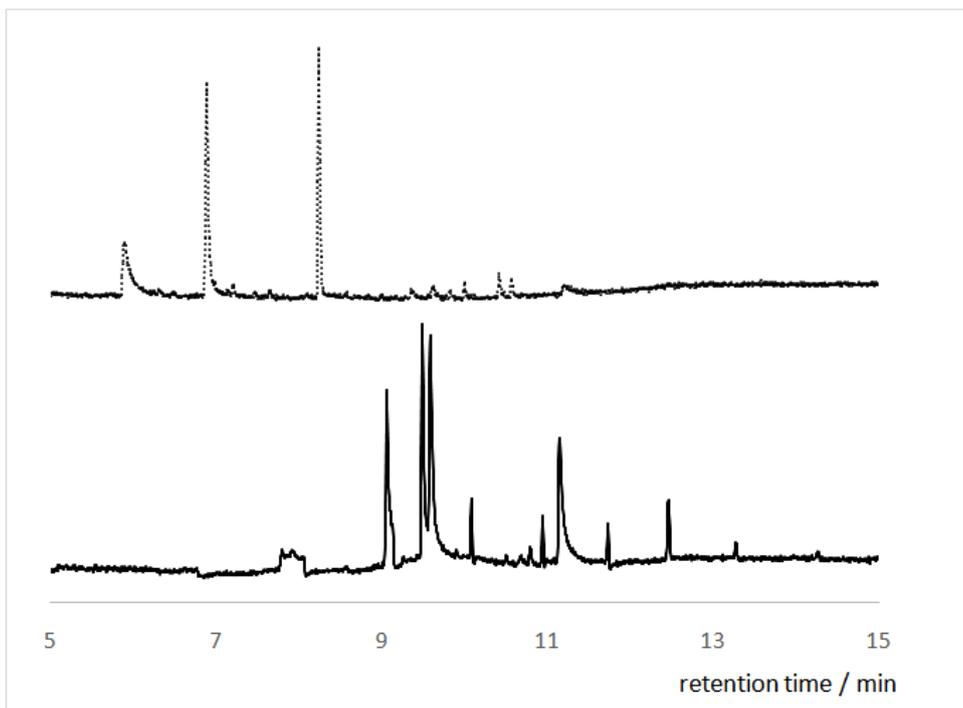


Figure 4. Degradation of 4-MAA, AA and DMAA with ozone. Bottom: 4-MAA, AA and DMAA solution, top: after 10 min bubbling with ozone

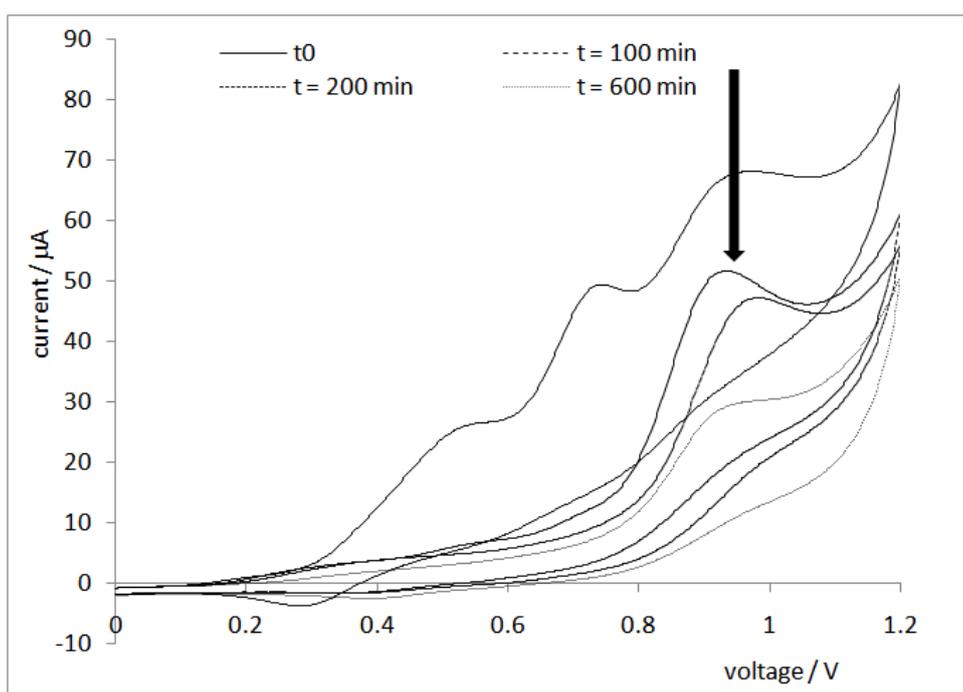
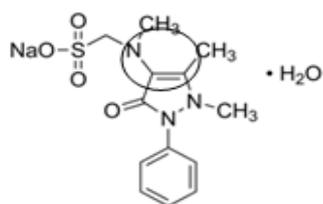


Figure 5. Cyclic voltammogram of metamizol at different electrolysis times

At about 0.5 V and 0.6 V, the enamine moiety ($-C=C-N-$, see the circle in the structure)



oxidises and forms an iminium radical cation. In the reversed scan, a small cathodic peak can be observed at 0.3 V. After Bacil et al. [13,14], the oxidised metamizole can subsequently react (dimerize) at 0.5 V (EC mechanism). The oxidation process at 0.9 V is common to all antipyrines. Therefore, the most plausible oxidation possibility is the nitrogen adjacent to the phenyl ring.

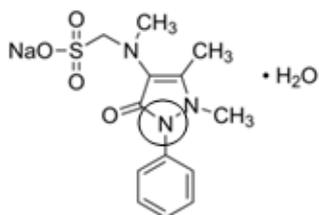


Figure 6 shows the GCMS after different electrolysis times: after 100 min 4-MAA, AA and DMAA are already significantly decreased, and products with lower retention times appear. Only three and two products appear after 600min and 10,000 min, respectively. According to Figure 5 the product after 600 min with about 8.3 min retention time (see star in Figure 6) may be an aniline derivate. The mass spectra (Figure 7) indicate that the two peaks for retention times lower than 7 min in Figure 4 and Figure 6 are the same. The peaks correspond to those identified by Perez-Estrada [12] and exhibit nearly the same fragmentation pattern (see Table 1). The only difference is the fragment mass (m/z 150) of the substance at 6.9 min.

Table 1. Parent ion and fragments (incl. structures) of the peaks at 5.9 min and 6.9 min

retention time / min	Mw parent ion / m/z	mass fragments /m/z
5.9	164	121, 107, 92, 77, 65, 43
6.9	164	150, 121, 107, 92, 77, 65, 43
mass /m/z	structure	
164	 (1-Methyl-2-Phenyl) Hydrazide	
164	 (1-Methyl-2-Acyl, 2'-Phenyl) Hydrazine	
150	 or	
121	 Phenylformamide [12]	
107		
92		
77		
43	 CH_3CO	

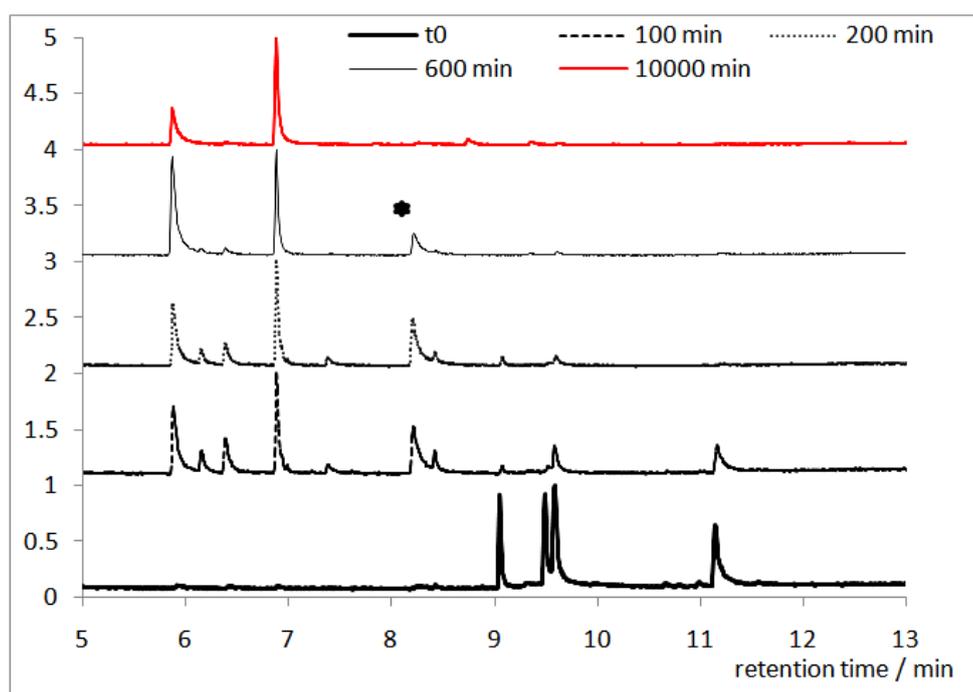


Figure 6. GCMS spectra of 4-MAA, AA and DMAA after different electrolysis times

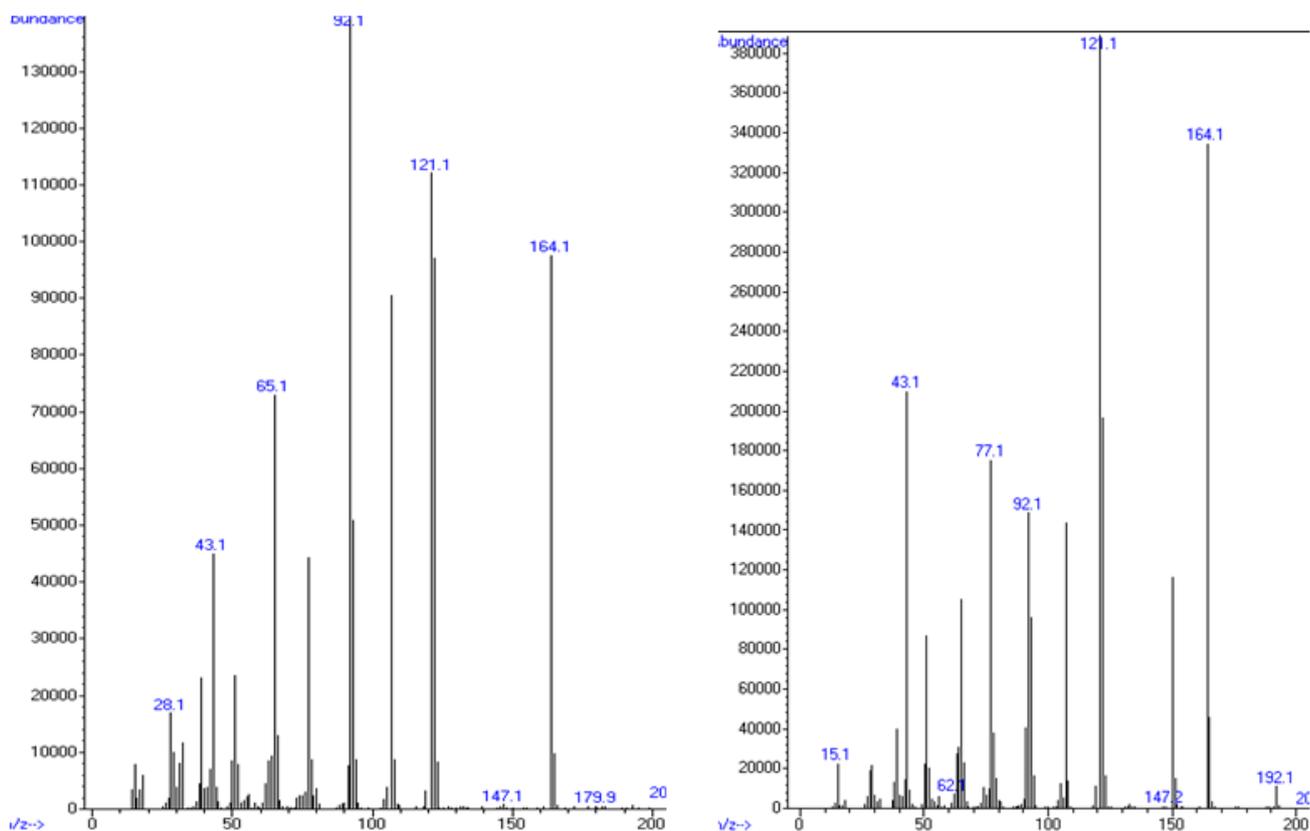


Figure 7. EI-mass spectra of the peaks at 5.9 min and at 6.9 min

4.3. Reduction in the Gas Phase

Aristov and Habekost describe the reductive degradation procedure in detail [15,16]. Therefore, only a few fundamental aspects are described here: The flow reactor is a V2a stainless steel tube 700 mm long and 18 mm dia. The reduction reagent was reduced iron powder, which was gently mixed with glass wool until a homogeneous fluffy powder was obtained. This was

poured into the tube to a length of about 200 mm. The reactor was heated in a hinged tube furnace. The metamizol / methanol mixture was injected via a syringe controlled by a stepping motor. The whole injection time was about 10 s. A nitrogen stream with a flow rate of 10 mL/min transported the metamizol solution into the reactor. The products were condensed in a cooling trap and analysed with a GC-MS in scan mode. Figure 8 shows the experimental setup.

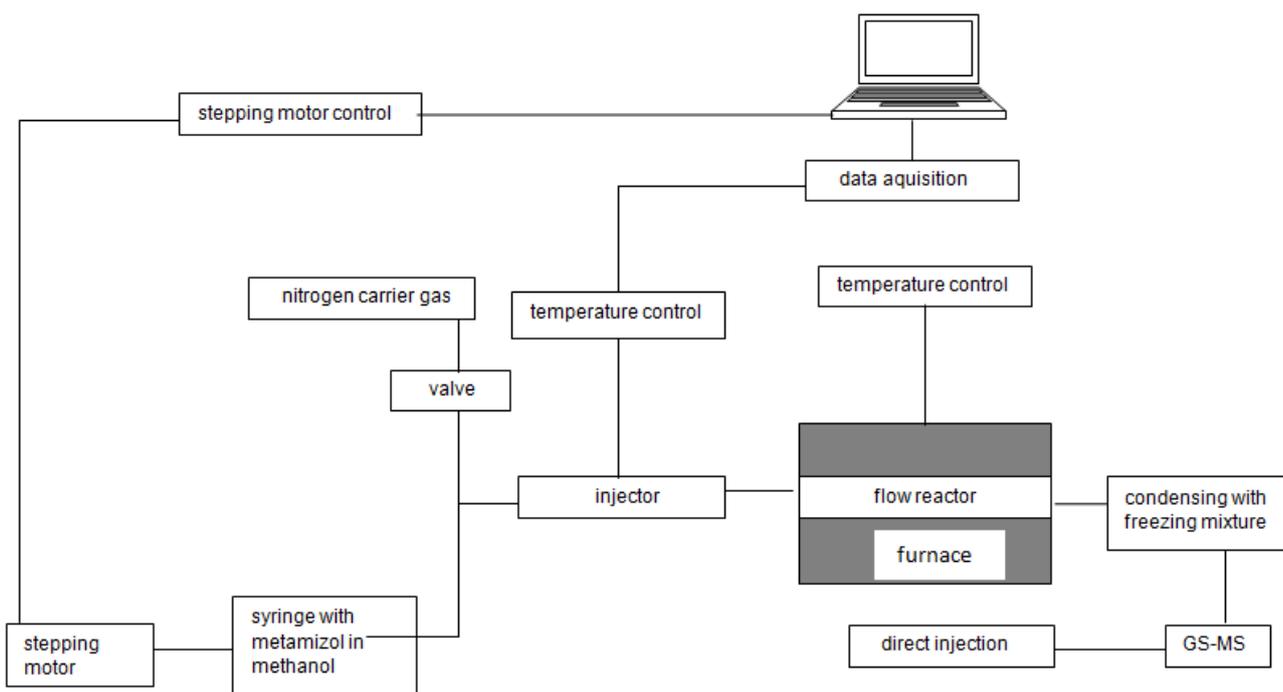


Figure 8. Experimental setup for reductive degradation of metamizol

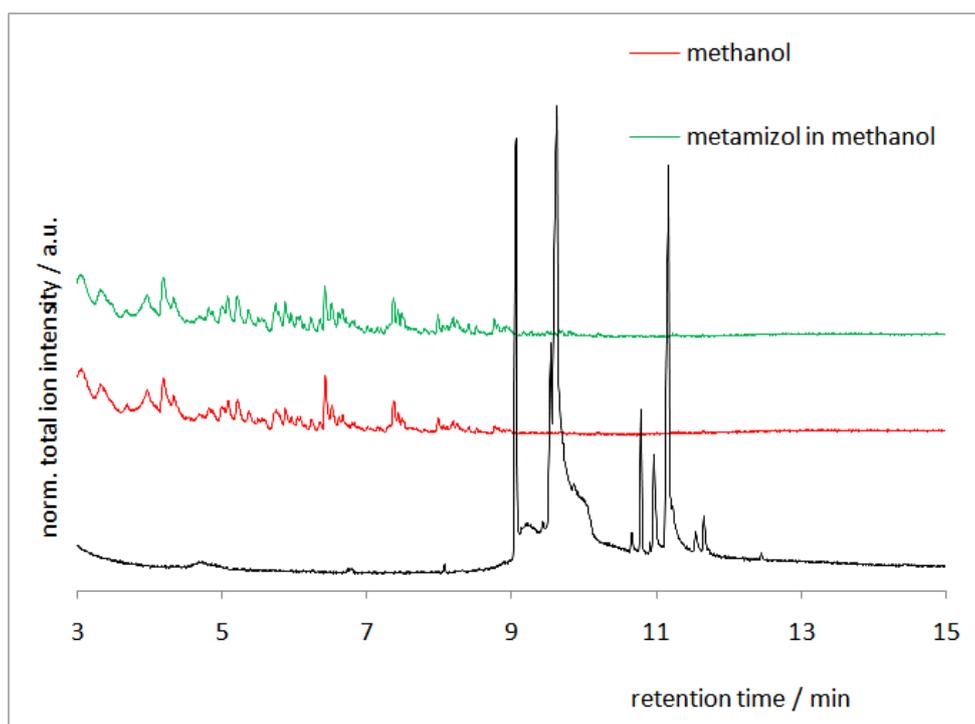


Figure 9. Reductive degradation of metamizol. Bottom: direct injection; middle: methanol at 500°C reactor temperature; top: metamizol in methanol at 500°C reactor temperature

Figure 9 shows the resulting GC at different temperatures. The GC-MS shows a significant degradation of metamizol at 500°C with a conversion rate of better than 99%.

The difference between the solvent methanol and the solution metamizol in methanol shows that the background in the GC results from the solvent itself. Unfortunately, we were not able to measure the total organic compounds (TOC).

5. Discussion

This paper (the author's second investigation of metamizol in this journal) has described different methods for degrading metamizol: oxidative, electrochemical and reductive processes. The results show that the most effective method is (oxygen-free) reduction of metamizol at about 500°C. The products and degradation rate were identified via GCMS. In our further work, we will test whether all metabolism products can be degraded via gas phase reduction of contaminated wastewater or urine, and whether there are any cross-sensitivities.

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References

- [1] S. Wiegel, A. Auling, R. Brockmeyer, H. Harms, J. Löffler, H. Reineke, R. Schmidt, B. Stachel, W. von Tumpling, A. Wanke, *Pharmaceuticals in the river Elbe and its tributaries*, *Chemosphere*, 57, 107- (2004).
- [2] E.Z. Katz, L. Granit, M. Levy, *Formation and excretion of dipyrone metabolites in man*, *Eur. J. Clin. Pharmacol.* 42, 187-191 (1992).
- [3] V.V. Arkhipchuk, V.V. Goncharuk, V.P. Chernykh, L.N. Maloshtan, I.S. Gritsenko, *Use of a complex approach for assessment of metamizol sodium and acetylsalicylic acid toxicity, genotoxicity and cytotoxicity*, *J. Appl. Toxicol.* 24, 401-407 (2004).
- [4] A.S. Giri, A.K. Golder, *Fenton, Photo-Fenton, H₂O₂ Photolysis, and TiO₂ Photocatalysis for Dipyrone Oxidation: drug Removal, Mineralization, Biodegradability, and Degradation Mechanism*, *Ind. Eng. Chem. Res.* 53, 1351-1358 (2014).
- [5] W.R.P. Baros, M.P. Borges, R.M. Reis, R.S. Rocha, R. Bertazzoli, M.R.V. Lanza, *Degradation of Dipyrone by the Electro-Fenton Process in an Electrochemical Flow Reactor with a Modified Gas Diffusion Electrode*, *J. Braz. Chem. Soc.* 22, 1673-1680 (2014).
- [6] W.R.P. Baros, M.P. Borges, J.R. Steter, J.C. Forti, R.S. Rocha, M.R.V. Lanza, *Degradation of Dipyrone by Electrogenerated H₂O₂ Combined with Fe²⁺ Using a Modified Gas Diffusion Electrode*, *J. Electrochem. Soc.* 161, H867-H873 (2014).
- [7] R.M. Reis, J.A.F. Baio, F.L. Migliorini, R. da Silva Rocha, M.R. Baldan, N.G. Ferreira, M.R. de Vasconcelos Lanza, *Degradation of dipyrone in an electrochemical flow-by reactor using anodes of boron-doped diamond (BDD) supported titanium*, *J. Electroanal. Chem.* 690, 89-95 (2013).
- [8] M.H.M.T. Assumpcao, A. Moraes, R.F.B. De Souza, R.M. Reis, R.S. Rocha, I. Gaubeur, M.L. Calegario, P. Hammer, M.R.V. Lanza, M.C. Santos, *Degradation of dipyrone via advanced oxidation processes using a cerium nanostructured electrocatalyst material*, *Appl. Catal. A: General* 462-463, 256-261 (2013).
- [9] V.R. Chelli, A.K. Golder, *Ag-doping on ZnO support mediated by bio-analytes rich in ascorbic acid for photocatalytic degradation of dipyrone drug*, *Chemosphere* 208, 149-158 (2018).
- [10] L. de Melo da Silva, F. Gozzi, I. Sires, E. Brillias, S.C. de Oliveira, A.M. Junior, *Degradation of 4-aminoantipyrine by electro-oxidation with boron-doped diamond anode: optimization by central composite design, oxidation products and toxicity*, *Sci. tot. Environ.* 631-632, 1079-1088 (2018).
- [11] A. Habekost, *The Analgesic Metamizol (Dipyrone) and Its Related Products Antipyrine, 4-Aminoantipyrine and 4-Methylaminoantipyrine. Part 1: Mass Spectrometric and Electrochemical Detection*, *World J. Chem. Educ.* 6, 134-144 (2018).
- [12] L.A. Perez-Estrada, S. Malato, A. Agüera, A.R. Fernandez-Alba, *Degradation of dipyrone and its main intermediated by solar AOPs. Identification of intermediate products and toxicity assessment*, *Catal. Today*, 129, 207-214 (2007).

- [13] R.P. Bacil, R.M. Buoro, O.S. Campos, M.A. Ramos, C.G. Sanz, S.H.P. Serrano, *Electrochemical behavior of dipyrrone (metamizol) and others pyrazolones*, *Electrochim. Act.* 273, 358-366, (2018).
- [14] R.P. Bacil, R.M. Buoro, R.P. da Silva, R.P., D.B. Medinas, A.W.G. Lima, S.H.P. Serrano, *Mechanism of electro-oxidation of metamizol using cyclic voltammetry at a glassy carbon electrode*, *ECS Trans. Electrochem. Soc.* 43, 251-258 (2012).
- [15] N. Aristov, A. Habekost, *Heterogeneous dehalogenation of PCBs with iron/toluene or iron/quicklime*, *Chemosphere* 80, 113-115, (2010).
- [16] A. Habekost, N. Aristov, *Heterogeneous reductive dehalogenation of PCB contaminated transformer oil and brominated diphenyl ethers with zero valent iron*, *Chemosphere* 88, 11, 1283-1287 (2012).