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Influence of carboxylic group or methyl ester group on the interactions of copper cation with aromatic system of naproxen, naphthalene acetic acids and their methyl esters

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ABSTRACT

Solutions containing naproxen, its methyl ester and Cu^{2+}, or naphthalene acetic acid, its methyl ester and Cu^{2+} was analyzed by using electrospray ionization mass spectrometry. As a result of interaction between Cu^{2+} and aromatic system (Cu^{2+}–π interaction), the respective molecular ions were obtained. The interactions of Cu^{2+} with –COOH and $–COOCH_3$ groups compete with that of Cu^{2+} with naphthalene rings, affecting the formation of molecular ions. Because of inductive effect of $–CH_3$ moiety, $–COOCH_3$ group interacts with Cu^{2+} stronger than –COOH group. ESI mass spectrum obtained for a mixture of isotopically labeled 1-naphthalene acetic acid methyl ester, 2-naphthalene acetic acid methyl ester and Cu^{2+} showed that second isomer is more prone to form molecular ions than the first.

1. Introduction

Copper complexes with non-steroidal anti-inflammatory drugs (e.g. with naproxen, **Nap**, Scheme 1) may show interesting pharmaceutical properties [1,2], e.g. **Nap**–Cu complexes are potential superoxide dismutase mimics [3]. Therefore, the study of physicochemical properties of such complexes is of importance.

Copper complexes with **Nap** are formed as a result of interactions between Cu and deprotonated carboxylic group of **Nap**, as demonstrated by a number of authors [4–10]. However, naproxen has a naphthalene ring; therefore, some interaction between Cu and aromatic system (Cu^{2+}–π interaction) is expected. Upon electrospray ionization (ESI) conditions, a result of such interaction may be formation of a molecular ion [11–13], in this case ion $[\mathbf{Nap}]^{+\bullet}$. Obviously ion $[\mathbf{Nap}]^{+\bullet}$ is formed by the interaction of neutral naproxen molecule (not deprotonated molecule $[\mathbf{Nap}\text{-H}]^-$) with Cu^{2+} (e.g. through the reaction $\mathbf{Nap} + Cu^{2+} \rightarrow [\mathbf{Nap}]^{+\bullet} + Cu^+$). However, part of naproxen is dissociated (exist as $[\mathbf{Nap}–H]^-$ anion); therefore it is expected that the formation of molecular ion of methyl ester of naproxen (ion $[\mathbf{NapCH_3}]^{+\bullet}$) will be more efficient than that of ion $[\mathbf{Nap}]^{+\bullet}$. As described further in the text, the opposite situation was observed. Taking into account the importance of Nap–Cu complexes, the interaction between naproxen molecule (or its ester) and copper cation is worth studying, and formation of respective molecular ions allow getting some insight in the nature of this interaction.

2. Experimental

Naproxen and naphthaleneacetic acids were obtained from Sigma-Aldrich (Poznań, Poland). The corresponding esters were synthesized as follows: 200 mg of particular acid were dissolved in 10 ml of methanol (Sigma-Aldrich) and then 0.5 ml of thionyl chloride (Fluka) was added. The solutions were heated under reflux for 1 h and concentrated on a rotary evaporator. The non-volatile residue was dissolved in 5 ml of ethyl ether (Sigma-Aldrich), washed with saturated sodium bicarbonate (POCh) water solution, dried over sodium sulfate (Chempur), filtered and finally the solvent was removed on a rotary evaporator. Similar procedures were used for isotopically labeled esters, but smaller amounts, i.e. 100 mg, 3 ml and 0.25 ml of acids, CD_3OD and thionyl chloride, respectively, were used.

In order to obtain ESI mass spectra, the sample solutions were prepared in methanol. Concentration of copper salt was constant, namely 10^{-4} mol/dm^3. The spectra were obtained for different concentrations of acid and ester, and representative examples were

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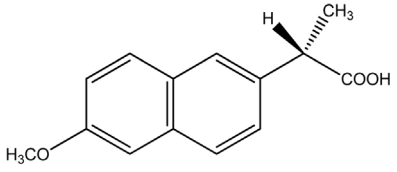

Scheme 1. Naproxen (**Nap**).

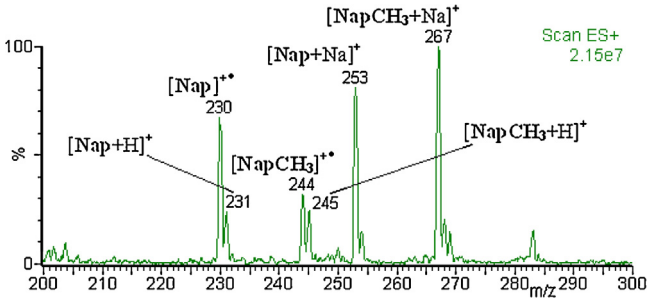

Fig. 1. ESI mass spectrum obtained for solution containing **Nap**, methyl ester of naproxen (**NapCH$_3$**) and $CuBr_2$, [**Nap**]$^{+\bullet}$ 1.45e7 ± 1.2e5, [**NapCH$_3$**]$^{+\bullet}$ 6.93e6 ± 0.6e5 (obviously, signals of ^{13}C-containing ions [**Nap**]$^{+\bullet}$ and [**NapCH$_3$**]$^{+\bullet}$ overlap with signals of protonated molecules, but there are no doubts that protonated molecules were detected).

selected for Figs. 1–3. Different copper salts were tested ($CuCl_2$, $CuBr_2$, $Cu(NO_3)_2$, $CuSO_4$, $Cu(ClO_4)_2$); however, the counter ion does not influence the formation of the molecular ions discussed.

The ESI mass spectra were obtained on a Waters/Micromass (Manchester, UK) ZQ2000 mass spectrometer (single quadrupole type instrument, Z-spray, software MassLynx V3.5). The sample solutions were infused into the ESI source using a syringe pump, and the flow rate was 80 μl/min. The ESI source potentials were as follows: capillary 3 kV, lens 0.5 kV, extractor 4 V and cone voltage (CV) 10–15 V. Cone voltage has the most profound effect on the mass spectra obtained. Increase in this parameter leads to the so-called "in-source" fragmentation/dissociation but a too low cone voltage may cause a decrease in sensitivity. The cone voltage value 10–15 V was low; however, already at 20 V there were quite abundant fragment ions (e.g. for naproxen at *m/z* 185 [14,15]). Therefore,

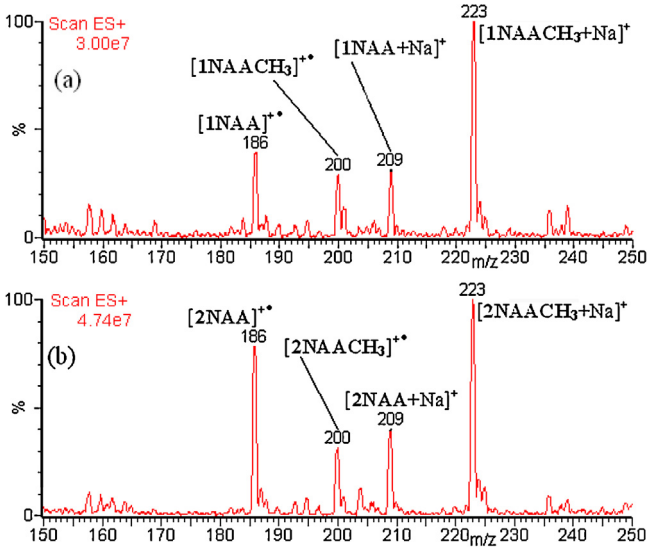

Fig. 2. ESI mass spectra obtained for solutions containing 1-naphthaleneacetic acid (**1NAA**), its methyl ester (**1NAACH$_3$**) and $CuCl_2$, [**1NAA**]$^{+\bullet}$ 1.19e7 ± 0.9e5, [**1NAACH$_3$**]$^{+\bullet}$ 8.74e6 ± 0.7e5 (a); 2-naphthaleneacetic acid (**2NAA**), its methyl ester (**2NAACH$_3$**) and $CuCl_2$, [**2NAA**]$^{+\bullet}$ 3.72e7 ± 3.4e5, [**2NAACH$_3$**]$^{+\bullet}$ 1.5e7 ± 1.3e5 (b).

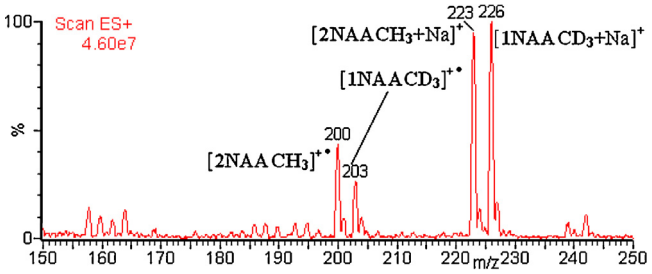

Fig. 3. ESI mass spectrum obtained for solution containing **1NAACD$_3$** (α isomer), **2NAACH$_3$** (β isomer) and $CuCl_2$ ([**2NAACH$_3$**]$^{+\bullet}$ 2.01e7 ± 1.6e5, [**1NAACD$_3$**]$^{+\bullet}$ 1.22e7 ± 1.0e5.

in order to limit the gas phase processes to minimum, the cone voltage was 10–15 V (sensitivity for the ions of interest was satisfactory). The source temperature was 120 °C and the desolvation temperature was 300 °C. Nitrogen was used as the nebulizing and desolvating gas at the flow-rate of 100 and 300 l h^{-1}, respectively.

The mass spectra (Figs. 1–3) are shown in the *m/z* range of interest. It has to be stressed that in the higher *m/z* range, the signals of copper complexes with naphthalene conjugates used (e.g. [**Nap** + CuCl]$^+$ at *m/z* 328) were characterized by very low abundances in comparison to the abundances of ions discussed. In the lower *m/z* range there were no doubly charged ions (e.g. [**Nap** + Cu]$^{2+}$ *m/z* 146.5, potential precursor of ion [**Nap**]$^{+\bullet}$). Thus, the discussed molecular ions are formed immediately upon the transfer of ions from the solution to the gas phase or already in the charged droplets.

The mass spectra shown in Figs. 1–3 were generated by averaging of 10 mass spectra. The absolute intensities (in arbitrary units) of the highest displayed peak are shown in top right or left corner. The intensities of the peaks of ions of interest (molecular ions) and calculated standard deviation are shown in captions of the figures.

3. Results and discussion

Fig. 1 shows the ESI mass spectrum obtained (in positive ion mode) for the solution containing **Nap**, methyl ester of naproxen (**NapCH$_3$**) and $CuBr_2$ at the concentrations 2×10^{-5} mol/dm^3, 5×10^{-6} mol/dm^3 and 10^{-4} mol/dm^3, respectively (it is clear that in order to generate positive ions from naproxen and its methyl ester with comparable abundances, concentration of the former has to be higher than that of the latter). The discussed further positive ions are formed due to the proton or sodium attachment to the neutral molecule or electron detachment from it.

Concentration of **Nap** is four times higher than that of **NapCH$_3$**, but the signals of protonated and sodiated molecules of **Nap** are not more intensive than those of protonated and sodiated molecules of **NapCH$_3$** ([**Nap** + H]$^+$ ≈ [**NapCH$_3$** + H]$^+$, [**Nap** + Na]$^+$ < [**NapCH$_3$** + Na]$^+$). However, the signal of naproxen molecular ion is definitely more intensive than that of naproxen methyl ester molecular ion ([**Nap**]$^{+\bullet}$ > [**NapCH$_3$**]$^{+\bullet}$, Fig. 1). Such an effect of naproxen esterification is unexpected since organic acids usually have higher ionization energies than their esters (http://webbook.nist.gov/chemistry/) and, as mentioned earlier, part of naproxen is dissociated.

The molecular ions [**Nap**]$^{+\bullet}$ and [**NapCH$_3$**]$^{+\bullet}$ are formed as a result of the interaction of naphthalene ring of **Nap** and **NapCH$_3$** molecules with Cu^{2+}. The interactions of Cu^{2+} with –COOH and –$COOCH_3$ groups (for **Nap** and **NapCH$_3$**, respectively) compete with that of Cu^{2+} with naphthalene rings. It is reasonable to assume that because of inductive effect of –CH_3 moiety [16], –$COOCH_3$ group interacts with Cu^{2+} stronger than –COOH group. As a consequence ion [**NapCH$_3$**]$^{+\bullet}$ is less abundant than ion [**Nap**]$^{+\bullet}$ (Fig. 1).