Nitrosation of Mefenorex in the Presence of Cyclodextrins*

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Abstract. β- and γ-Cyclodextrin (CD) and heptakis-2,6-di-O-methyl-β-cyclodextrin (DIMEB) form soluble inclusion compounds with mefenorex (MEF); with α-CD a partial inclusion occurs. No solid inclusion compound could be obtained with the four CDs, β-, γ-CD and DIMEB, but not α-CD, enhance the nitrosation rate of MEF if the nitrosation assay procedure (NAP test) is applied. During this reaction with β- and γ-CD, solid inclusion compounds of the CDs and nitrosomefenorex (NMEF) precipitate.

Key words: Nitrosation reactions: α-, β-, γ-cyclodextrin, dimethyl-β-cyclodextrin; mefenorex; nitrosomefenorex.

1. Introduction

The in vitro nitrosation rate of nitrosatable drugs can be influenced differently by α-, β- and γ-cyclodextrin (CD) and by heptakis-2,6-di-O-methyl-β-cyclodextrin (DIMEB). The reaction rates of the fast nitrosatable piperazine, ethambutol and cimetidine are not influenced by α-, β- and γ-CD [1]. But, β-, γ-CD and DIMEB catalyze significantly the nitrosation of the slower nitrosatable ephedrine [2] and fencamfamine [1]. With these two drugs the formation of solid inclusion compounds of β-CD and nitrosoephedrine [2] and of γ-CD and nitrosofencamfamine [1] has been observed.

It is the purpose of this paper to examine whether the in vitro nitrosation of the secondary amine mefenorex (MEF), a potent anorectic, to N-nitrosomefenorex (NMEF) can be enhanced by CDs.

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\begin{align*}
\text{Mefenorex (MEF)} & \quad \overset{\text{nitrosation}}{\rightarrow} \quad \text{N-Nitrosomefenorex (NMEF)} \\
\end{align*}
\]

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2. Materials and Methods

$\alpha$-CD: Aldrich Europe, Beerse; $\beta$-CD: Chinoin Co., Budapest; $\gamma$-CD: Nihon Shokuhin Kako Co., Tokyo. DIMEB: Prepared according to Szejtli et al. [3]; Fp. 311°C. The NMR spectrum corresponds to the specifications given by Casu et al. [4]. Mefenorex hydrochloricum: Homburg Co., Frankfurt/M.

The nitrosation procedure was performed with the nitrosation assay procedure (NAP test) as described before [1]. Solution I: mefenorex hydrochloricum 2.7301 g, HCl (37%) 0.5 ml, water to 500 ml; solution II: sodium nitrite 3.036 g to 100 ml water.

Inclusion compounds of $\beta$-CD or $\gamma$-CD and nitrosomefenorex: A solution of 50.0 mg $\beta$-CD or 57.1 mg $\gamma$-CD, respectively, in 2.0 ml solution I (37°C) are mixed vigorously with 200 µl solution II (37°C) in a small screw-topped 4.5-ml plastic tube. After 30 min the precipitate is centrifuged at 3000 rpm for 3 min. After decantation of the supernatant fluid the open plastic tubes were vacuum dried over calcium chloride at room temperature for 48 h. Yield: 30 mg white $\beta$-CD adduct, 40 mg $\gamma$-CD adduct.

$^1$H-NMR spectra were recorded on a 250 MHz spectrometer, WM 250 (Bruker Co., Karlsruhe) using 3-trimethylsilylpropionic acid-$d_4$-sodium as internal standard.

3. Results

3.1. FORMATION OF INCLUSION COMPOUNDS

The formation of CD-inclusion compounds with MEF and the formation of a nitroso-compound from MEF has not been reported up to now. It was not possible to obtain a solid inclusion compound with $\alpha$-, $\beta$- and $\gamma$-CD and DIMEB, respectively.

But all four CDs form soluble inclusion compounds with MEF, which could be proved by $^1$H-NMR. Table I shows the shifts of the CD protons in the presence of equimolar amounts of MEF and CDs. A shift of the protons H–3 and H–5, which are located in the inner part of the CD ring, indicates inclusion formation.

<table>
<thead>
<tr>
<th>CD-proton</th>
<th>$\alpha$-CD</th>
<th>$\gamma$-CD</th>
<th>DIMEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>H–1</td>
<td>0.0179</td>
<td>0.0107</td>
<td>0.0194</td>
</tr>
<tr>
<td>H–2</td>
<td>0.0237</td>
<td>0.0170</td>
<td>0.0290</td>
</tr>
<tr>
<td>H–3</td>
<td>−0.0251</td>
<td>−0.0022</td>
<td>−0.0757</td>
</tr>
<tr>
<td>H–4</td>
<td>0.0165</td>
<td>0.0177</td>
<td>0.0253</td>
</tr>
<tr>
<td>H–5</td>
<td>0.0139</td>
<td>−0.0090</td>
<td>−0.0172</td>
</tr>
<tr>
<td>H–6</td>
<td>0.0084</td>
<td>0.0044</td>
<td>−0.1078</td>
</tr>
</tbody>
</table>

MEF + $\alpha$-CD: Only H–3 is shifted to lower ppm values. This leads us to assume a partial inclusion of the aromatic moiety in the side $\alpha$ of the $\alpha$-CD molecule (Fig. 1).

MEF + $\beta$-CD: The sift of the protons to a higher field is so pronounced that an overlapping with the MEF protons occurs. Therefore, no NMR data could be obtained, but an inclusion of the MEF molecule is obvious from the spectrum.