Unusual Formation of Carbamate Salts: an Experimental Proof for the Mechanism of the Removal of Carbobenzyloxy Group by Catalytic Hydrogenolysis

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Z. Naturforsch. 33b, 1196-1197 (1978); received June 20, 1978

Carbamate Salts, Catalytic Hydrogenolysis

Catalytic hydrogenolysis of Z-Gly-NH₂ and Z-Ala-NH₂ resulted in the corresponding free amides and carbamate salts. This observation is a further experimental proof that carbamic acid derivatives are intermediates of hydrogenolytic removal of carbobenzyloxy group under neutral conditions. The ratio of the formation of the two compounds is dependent on the solvent, concentration and chemical structure. The carbamate salts can be acetylated without difficulties under the conditions of peptide bond formation.

The usual catalytic hydrogenolysis of Z-Gly-NH₂ [1] in methanol resulted in the desired H-Gly-NH₂ in 60%. During the process a very insoluble substance was precipitated on the palladised charcoal which was removed by washing with warm water, and a white, crystalline substance was obtained by evaporation of the aqueous solution. The elemental analysis and the quantitative evaluation of carbon dioxide liberated by acid showed that the compound consists of two equivalent of H-Gly-NH₂ and one equivalent of carbon dioxide. Its melting point of 125-126 °C agreed with that of carbamoylmethyl-ammonium-carbamylmethyl-carbamate ([H₂Gly-NH₂][O₂C-Gly-NH₂]) described by Holland [2] and previously considered by others to be carbonate salt [3]. The existence of the latter can be excluded because its aqueous solution does not result in precipitation of barium carbonate by addition of barium salts but it does by the effect of warming. Holland's experiment was repeated, too: the carbamate salt was precipitated from a solution of H-Gly-NH₂ in ethanol by addition of dry ice. Fig. 1 shows the products of catalytic hydrogenolysis of Z-Gly-NH₂.

Because of slight solubility of the carbamate salt in methanol it could be simply separated from H-Gly-NH₂. This enabled us to examine how the concentration and the quality of the solvents affected the ratio of the formation of the two products (Table I).

On the basis of these results it can be concluded that the ratio of the formation of the products is influenced by both the concentration and the quality of the solvent. Dependence of this ratio on the chemical structure has been shown, too. A 10% solution of Z-Ala-NH₂ [4] hydrogenated in methanol only resulted in isolation of the appropriate carbamate salt with a yield of 81.5% (m.p. 149-150 °C, good elementary analysis for CO₂, C, H and N, IR(KBr): 3000-2000 cm⁻¹) complex series of bands νNH₃, 1520 cm⁻¹ νCOO⁻, the IR-spectra is very similar to that of the carbamate salt of H-Gly-NH₂. Under the same conditions the carbamate salts of H-Val-NH₂, H-Phe-NH₂, H-Pro-NH₂ and H-Pro-NH₂ could not be isolated.

The question arose whether the carbamate salts cause difficulties during peptide couplings. Therefore, one equivalent of carbamate salt of H-Gly-NH₂ and 2.2 equivalents of Boc-Ala-OPFP [5] were reacted in the presence of two equivalents of triethylamine. The desired Boc-Ala-Gly-NH₂ was isolated in a yield of 85.8% (m.p. 133-134 °C, Rf 0.40 in a mixture of ethyl acetate/pyridine/acetic acid/water 240:20:6:11 on Kieselgel G nach Stahl, [α]D°: −7.8° (c=1.0, ethanol), good elementary analysis for C, H and N). Thus, carbamate salts can be acylated under suitable conditions*. This may explain why the formation of carbamate salts under

*Itoh reported the acylation of triethylammonium carbamate salts of amino acids and peptides in aqueous solution [6].

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Table I. Per cent amounts of the isolated products during catalytic hydrogenolysis of Z-Gly-NH₂.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration w/v[%]</th>
<th>Reaction time [h]</th>
<th>Isolated amount of product [mol %]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-Gly-NH₂</td>
<td>Carbamate salt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeOH</td>
<td>10</td>
<td>2-6</td>
<td>60.4</td>
</tr>
<tr>
<td>MeOH</td>
<td>4</td>
<td>2-6</td>
<td>94.5</td>
</tr>
<tr>
<td>H₂O</td>
<td>10</td>
<td>4</td>
<td>21.7</td>
</tr>
<tr>
<td>DMP</td>
<td>10</td>
<td>8</td>
<td>46.0</td>
</tr>
</tbody>
</table>

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the conditions given has escaped the notice of researchers so far.

The above results are further experimental proof that carbamic acid derivatives are intermediates of hydrogenolytic removal of the carboxy group under neutral conditions, too.

In consequence the carbamate salt formation should be always considered, when carboxy group of a peptide is removed by catalytic hydrogenolysis under neutral conditions, but it does not seem to disturb the concomitant coupling reaction.