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## Hydroxy- and aminomethylation reactions in the formation of oligomers from L-tyrosine and formaldehyde in basic medium

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### ABSTRACT

The study of the reaction of L-tyrosine or its tetrabutylammonium salt with formaldehyde was performed. The results established that this reaction does not lead to macrocyclic amino acid-type compounds, and in all cases, mixtures of linear oligomers of two or more L-tyrosine units bound by methylene groups were obtained. The formation of ion pair-type linear aggregates in the tetrabutylammonium salt hinders the oligomerization reaction, allowing the isolation of an L-tyrosine dimer, unlike the L-tyrosine reaction, in which a trimer could be isolated.

In this Letter, the behavior of different L-tyrosine derivatives with formaldehyde is analyzed, and the conditions that direct the reaction course toward macrocyclic or linear compounds are discussed.

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Cyclophanes are macrocyclic compounds that contain two or more aromatic units bonded in *meta* or *para* positions by small spacers.<sup>1,2</sup> Recently, the design and synthesis of this type of molecules have attracted the attention of chemists due to its usefulness in the selective recognition of molecules of chemical and biological importance.<sup>3–7</sup>

Azacyclophanes are macrocycles that combine the electron donor and acid–base properties of nitrogenated heterocycles with the properties of cyclophanes. The combination of these properties, along with its conformational rigidity, causes this type of compound to be of interest for the study of host–guest processes.<sup>1,8,9</sup>

Recently, our research group developed a simple method for the synthesis of azacyclophanes called macrocyclic amino acids (benzoxazinephanes) using a double aromatic Mannich-type reaction between esters derived from L-tyrosine and formaldehyde (Scheme 1).<sup>10–13</sup>

To obtain water-soluble azacyclophanes derived from tyrosine, the reaction between L-tyrosine **1** and formaldehyde was performed. This reaction did not lead to the expected azacyclophane **2**, but it produced a mixture of linear oligomers. From the product mixture, it was only possible to characterize a trimer composed of three units of L-tyrosine bound by two methylene groups **3** (Scheme 2).<sup>12</sup>

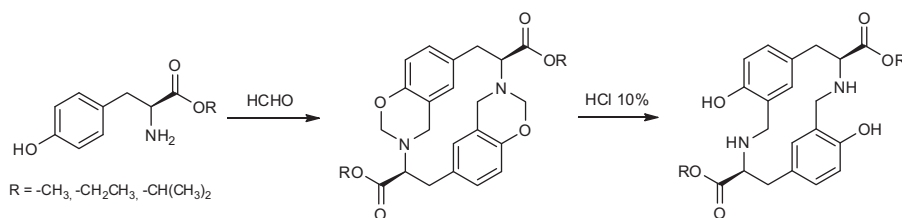
Sudo et al. have recently established that the Mannich reaction does not occur when it is performed using amino acids; however,

when the reaction is performed with the respective tetrabutylammonium salts in basic medium with *p*-cresol and formaldehyde, the corresponding 3,4-dihydro-2*H*-1,3-benzoxazines are obtained with good yields.<sup>14</sup> Continuing with our studies on the chemical reactivity of L-tyrosine derivatives with aldehydes, in this study, examination of the reaction of L-tyrosine or its tetrabutylammonium salt with formaldehyde was performed. The results established that both L-tyrosine and its tetrabutylammonium salt react with formaldehyde to form linear Mannich bases, and the formation of macrocyclic compounds was not observed in any of the cases. In this study, the behavior of these L-tyrosine derivatives with formaldehyde is analyzed, and the conditions that direct the reaction course toward macrocyclic or linear compounds are discussed.

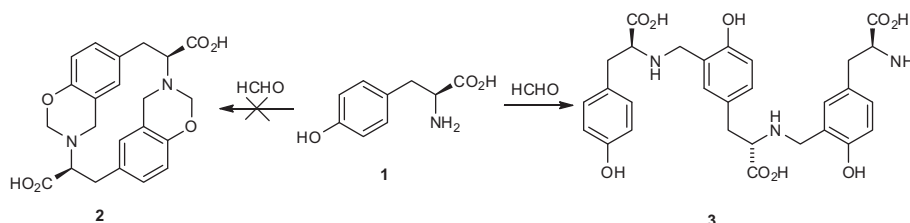
The first studies of the reaction between L-tyrosine and formaldehyde were performed during the mid-twentieth century, and it was established that L-tyrosine reacts with two equivalents of formaldehyde in alkaline medium to form high molecular weight compounds that were not characterized.<sup>15,16</sup> Recently, Quevedo et al. reported the synthesis of azacyclophanes from tyramine and L-tyrosine alkyl esters through a double aromatic Mannich-type condensation with formaldehyde in basic medium.<sup>10–13</sup> To determine the structure of the primary products of the reaction of L-tyrosine with formaldehyde, thus establishing whether the cyclophane-type macrocyclic compounds are obtained or the linear oligomeric structures are favored, examination of the reaction of L-tyrosine or its tetrabutylammonium salt derivative with formaldehyde in aqueous basic medium at room temperature

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**Scheme 1.** Synthesis of macrocyclic  $\alpha$ -amino esters and  $\alpha$ -amino acids from L-tyrosine.



**Scheme 2.** Synthesis of the linear trimer **3** by the reaction of L-tyrosine **1** with formaldehyde.

was performed in this study. The effects of the L-tyrosine concentration, the number of base equivalents, the amount of formaldehyde, and the reaction time were evaluated.

The synthesis of azacyclophanes has been reported by Quevedo et al. through a macrocyclization reaction of tyramine and L-tyrosine alkyl esters with formaldehyde performed in basic medium using small amounts of the base. To study the reaction of L-tyrosine and formaldehyde in aqueous medium, greater amounts of the base were used (1–2 equiv of NaOH) to solubilize the amino acid and to deprotonate the amine group in the zwitterionic form.

First, the reaction of L-tyrosine with formaldehyde was performed at room temperature using two equivalents of NaOH, excess formaldehyde, and 0.37 M L-tyrosine for 3 days.<sup>17</sup> The analysis of the <sup>1</sup>H NMR spectrum in D<sub>2</sub>O shows several groups of signals, allowing the proposal of structure **5** (Scheme 3). The signals between 6.87 and 6.32 ppm (m, 2H) are assignable to the aromatic protons in the *meta* position to the phenolic hydroxyl. In the region of 4.46–4.20 ppm (m, 2H), the signals corresponding to the –CH<sub>2</sub>– hydrogens of the hydroxymethyl groups bonded to the rings in the *ortho* position to the phenolic hydroxyl appear. The signals from the protons of the methylene bonded to the nitrogen of an L-tyrosine molecule and to the aromatic ring of another molecule appear at 3.94–3.51 ppm (m, 2H). The signals between 3.30 and 3.12 ppm (m, 1H) confirmed the presence of the proton bonded to the chiral carbon. The diastereotopic protons appeared at 2.78–2.21 ppm (m, 2H). Wide signals, such as multiplets, are observed in the spectrum, which most likely originated from a mixture of polymeric products with the general formula (C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub>)<sub>n</sub>, proposed based on the elemental analysis. Structure **5** coincides with the one previously reported by Brown in a study in which the experiment was performed with two equivalents of formaldehyde,<sup>15</sup> concluding that the excess formaldehyde does not affect the reaction course.

When the amount of NaOH added was decreased to one equivalent and two equivalents of formaldehyde and 0.49 M L-tyrosine were reacted for 6 days, the <sup>1</sup>H NMR spectrum presented signals that allowed the proposal of compound **6** as the primary product. In addition to the signals corresponding to the oligomer **6**, other signals of lower intensity are observed between 4.61 and 4.56 ppm (m), which are assignable to the benzoxazinic methylenes present in oligomer **7**, and the signals between 4.51 and 4.42 ppm (m) are attributable to the –CH<sub>2</sub>– hydrogens of the

methylene groups present in oligomer **5**. These results demonstrate that the isolated product corresponds to a mixture of oligomers **5**, **6**, and **7** (Scheme 3); in addition, they explain the differences in the C, H, and N percentages obtained by elemental analysis with respect to the calculated percentages for the primary product **6**. A comparison of the structure of product **6** (obtained in the reaction of L-tyrosine with formaldehyde and one equivalent of NaOH) with that of product **5** (obtained in the reaction using two equivalents of NaOH) reveals that the additional base equivalent improves the phenol nucleophilic character and favors another substitution in the *ortho* position to the phenolic hydroxyl.

When the reaction was performed under the same conditions as the previous experiment but with a decreased concentration of L-tyrosine, product **6** was also obtained as the primary product, and **5** and **7** were obtained as minor products.

In addition to the previous experiments, the reaction was performed with an excess of formaldehyde and different concentrations of L-tyrosine (0.39 M and 0.056 M), while maintaining the remaining conditions of the previous reactions. The isolated products from these tests behaved similarly to the ones obtained in the reactions using two equivalents of formaldehyde and L-tyrosine concentrations of 0.49 M and 0.058 M. The characterization by infrared spectroscopy and elemental analysis indicated that in both tests, the reaction leads to a mixture of oligomers **5**, **6**, and **7**, with **6** as the primary product.

The results of the study of the reaction between L-tyrosine and formaldehyde using one equivalent of NaOH and a reaction time of 6 days showed that the reaction course is not considerably altered with an excess of formaldehyde or lower concentrations of L-tyrosine. In all of the cases, a mixture of oligomers with structures **5**, **6**, and **7** was obtained (Scheme 3).

According to the observations of the previous reactions from the thin layer chromatography (TLC) monitoring, we decided to perform the reaction for 24 h using two equivalents of formaldehyde, one equivalent of NaOH, and 0.040 M L-tyrosine. At this reaction time, we observed the initial L-tyrosine, a more retained product and no considerable formation of the mixture of oligomers **5**, **6**, and **7** at the spotting point. To isolate the observed product, the reaction mixture was filtered to remove the non-reacted L-tyrosine, and the filtrate was adjusted to pH ~7 by the addition of 0.2 M HCl, causing the formation of a precipitate. The precipitate was filtered, washed with distilled water, and dried at 50 °C. Using

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