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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.

Cyclophanes are macrocyclic compounds that contain two or more aromatic units bonded in *meta* or *para* positions by small spacers.[1,2] 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.[3–7]

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.[1,8,9]

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).[10–13]

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).[12]

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-*2H*-1,3-benzoxazines are obtained with good yields.[14] 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.[15,16] 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.[10–13] 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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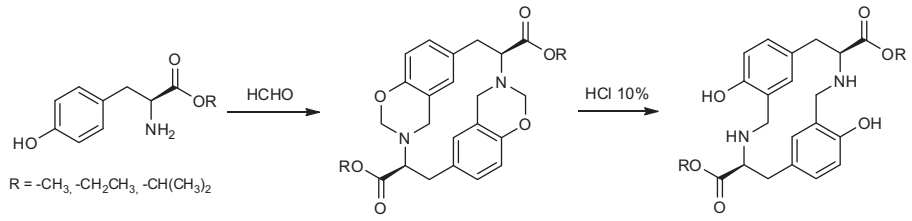
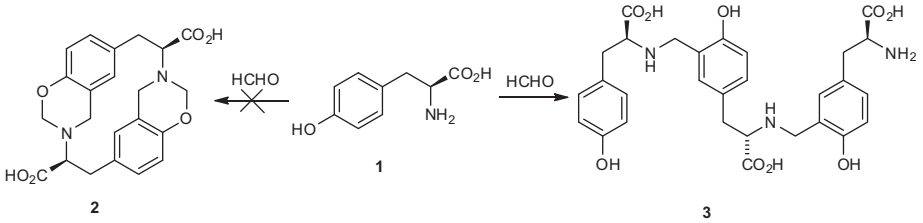


Scheme 1. Synthesis of macrocyclic α-amino esters and α-amino acids from L-tyrosine.



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.[17] The analysis of the ^{1}H NMR spectrum in D_2O 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_2– 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 $(C_{11}H_{13}NO_4)_n$, 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,[15] concluding that the excess formaldehyde does not affect the reaction course.

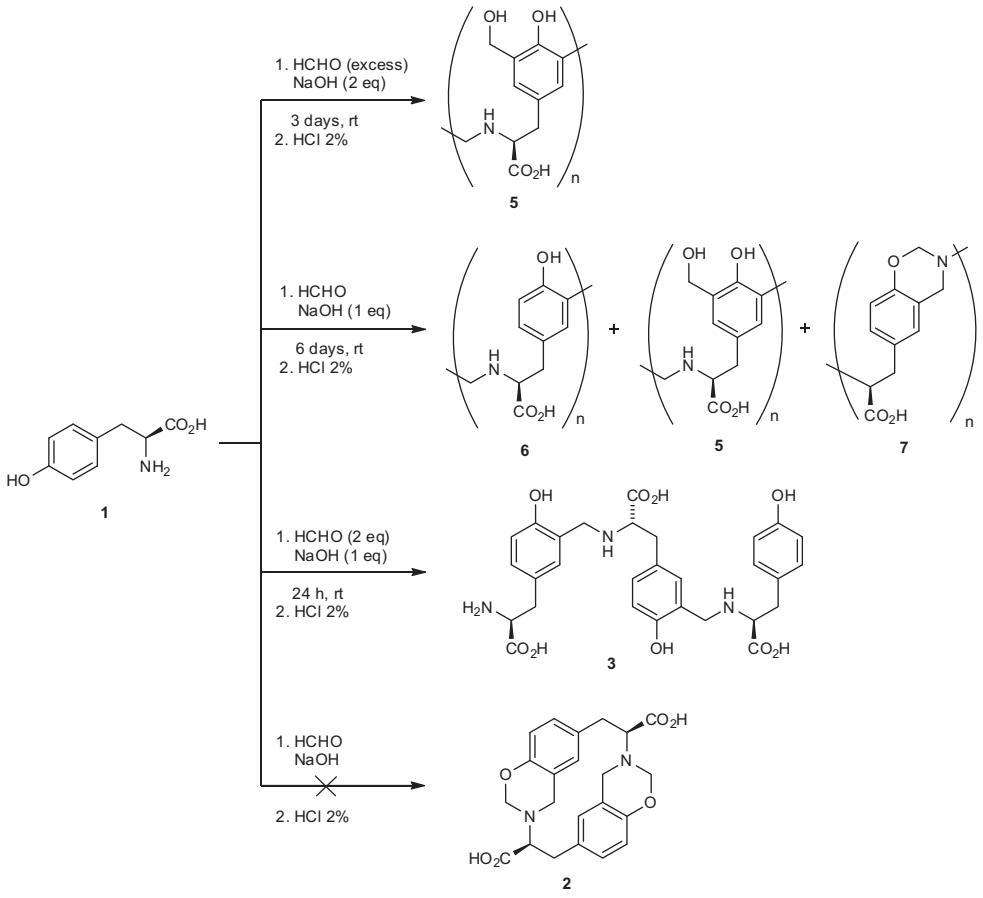
When the amount of NaOH added was decreased to one equivalent and two equivalents of formaldehyde and 0.49 M L-tyrosine were reacted for 6 days, the ^{1}H NMR spectrum presented signals that allowed the proposal of compound **6** as the primary product. In addition to the signals corresponding to the 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_2– 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

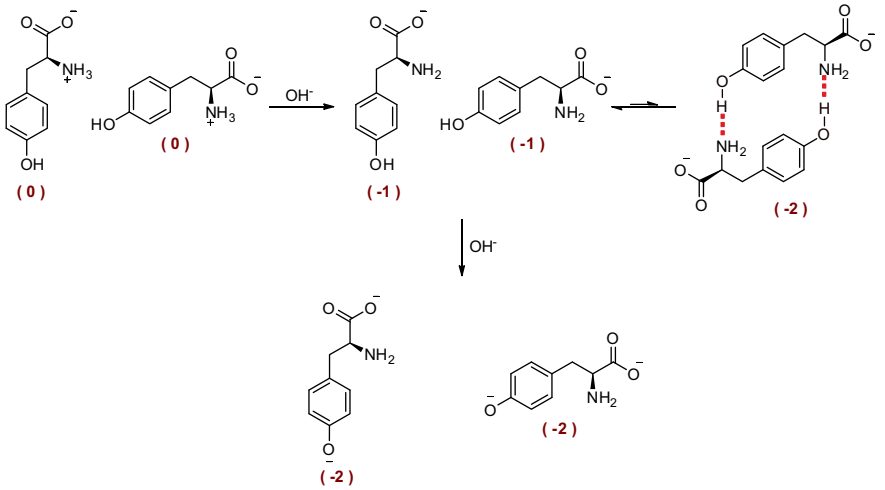


Scheme 3. Reaction of L-tyrosine with formaldehyde in basic medium.

this method, the previously reported compound **3** (Scheme 3) was isolated as a slightly yellow solid with a yield of 20%.[12]

Compound **3** is composed of three units of L-tyrosine bound by two methylene groups. The structure of this compound confirms that the compound mixture observed after 2 days of reaction performed under diluted conditions corresponds to oligomers of a few L-tyrosine units (for example, two, three, or four units). At longer reaction times, an increased number of L-tyrosine units are bonded together, forming products of several units with the general formula $(C_{10}H_{11}NO_3)_n$ (corresponding to **6**) that are retained at the spotting point of the silica gel chromatoplates.

All of the experimental reactions of L-tyrosine with formaldehyde in aqueous basic medium at room temperature resulted in obtaining of linear oligomers of structures **3**, **5**, **6**, and **7**; the formation of azacyclophane **2** (Scheme 3) was not observed in any of the cases. The attempts did not lead to macrocyclization, presumably due to the inability to form a pre-organized arrangement of the L-tyrosine molecules through hydrogen bonds in aqueous basic



Scheme 4. Proposed behavior of L-tyrosine in aqueous basic medium.

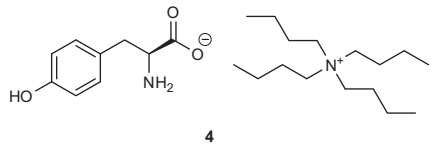


Figure 1. Structure of the tetrabutylammonium L-tyrosine salt **4**.

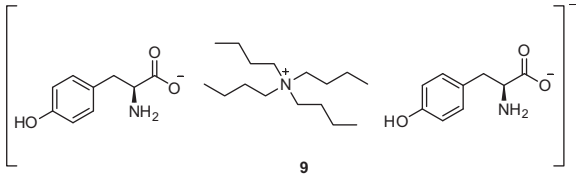


Figure 2. Structure of the $[C_{34}H_{56}N_3O_6]^-$ ion.

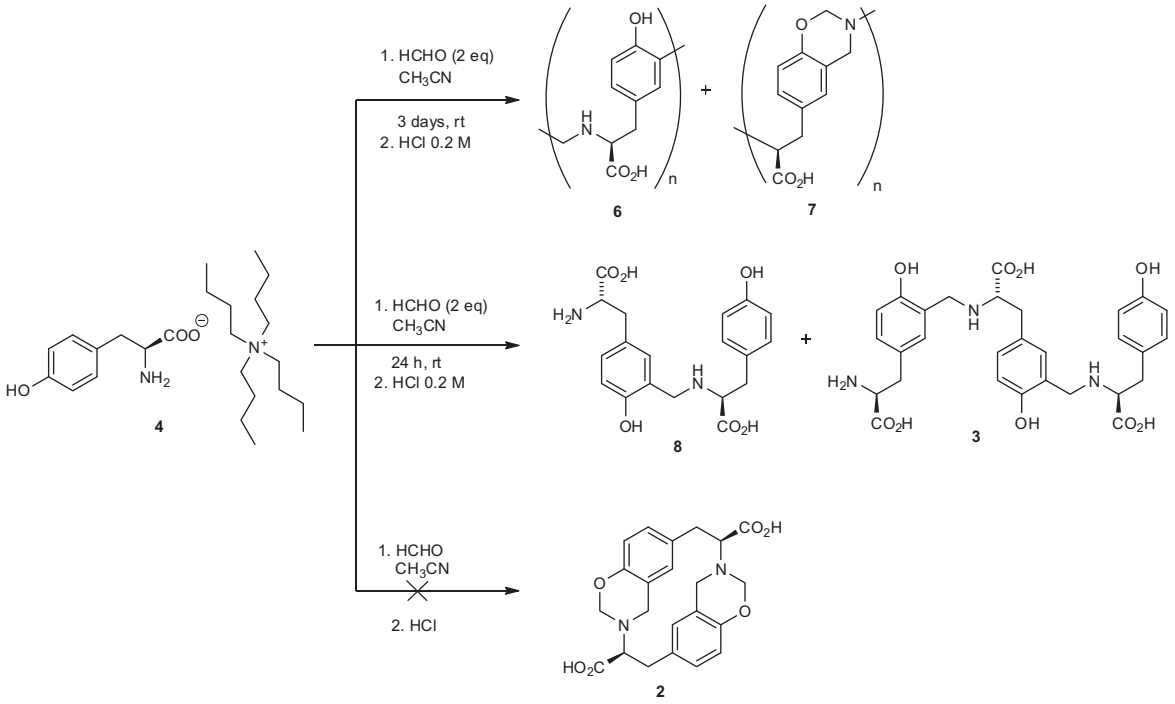
medium (Scheme 4), as previously demonstrated by computational calculations.[12] To study the reaction, it was necessary to add one or two equivalents of NaOH to improve the solubility of L-tyrosine in water and to deprotonate the amino group; however, this process results in a net negative charge on the molecules, which most likely causes the L-tyrosine anions with a −1 and −2 charge in aqueous medium to prefer being solvated by water molecules and to be separated from each other. According to this explanation, the model proposed to explain the macrocyclization reaction observed between L-tyrosine alkyl esters and formaldehyde is not favored in aqueous basic medium.

Considering that the quaternary ammonium salts of amino acids (especially the tetra-*n*-butylammonium salts) have the particular advantage of being soluble in organic solvents and have a free amino group, tetrabutylammonium L-tyrosinate **4** was synthesized, which is a quaternary ammonium salt of L-tyrosine, to study its reaction with formaldehyde in an organic solvent (Fig. 1).[18]

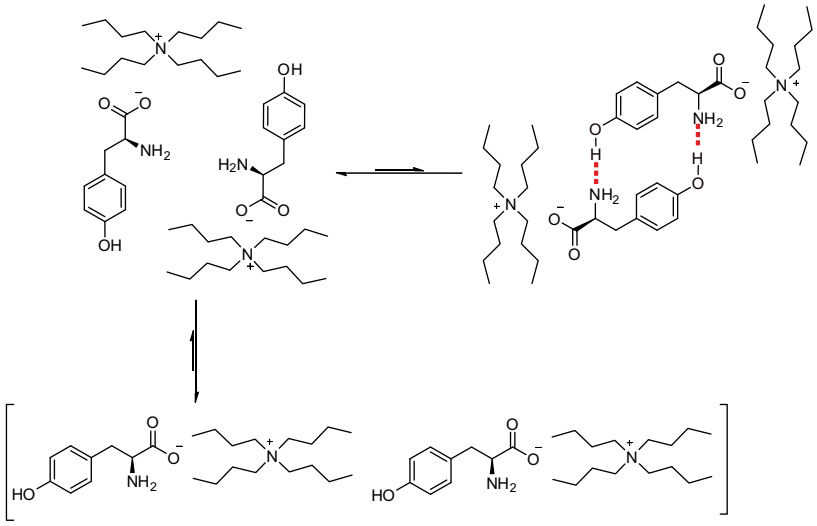
In this study, the characterization of compound **4** is reported for the first time, which was obtained as a cream-colored hygroscopic solid with a 98% yield. This compound melts with decomposition over the range of 148–153 °C and is soluble in acetonitrile and DMSO. The ESI-MS spectrum in the positive mode in CH_3CN showed the $[C_{16}H_{36}N]^+$ ion at *m*/*z* 242.10 (calculated: 242.28). In the negative mode, the $[C_9H_{10}NO_3]^-$ ion was found at *m*/*z* 179.75 (calculated: 180.07). Structure **4** was confirmed by elemental analysis and presented a monohydrate structure.

Given that **4** is soluble in acetonitrile, we decided to perform the reaction at room temperature in this solvent using two equivalents of formaldehyde at a 0.17 M concentration of **4** and a reaction time of 24 h.[19] The isolated product was a slightly yellow solid that melts over the range of 265–270 °C. The ESI-MS spectrum of this product in the negative mode primarily showed the $[C_{19}H_{22}N_2O_6\text{-}H]^-$ ion at *m*/*z* 373.00 (calculated: 373.14), corresponding to compound **8** (Scheme 5). In addition, the $[C_{29}H_{33}N_3O_9\text{-}H]^-$ ion was observed at *m*/*z* 566.30 (calculated: 566.21) as a peak of lower intensity, corresponding to compound **3**. These results indicated that the reaction of the tetrabutylammonium L-tyrosinate salt **4** with formaldehyde with a reaction time of 24 h leads to a mixture of oligomers of two and three units of L-tyrosine bound together by methylene groups (compounds **8** and **3**, respectively) (Scheme 5). The intensities of the peaks observed in the mass spectrum (ESI-MS) indicated that compound **8** is the primary product in the mixture. Contrary to the reaction of L-tyrosine in aqueous medium, an oligomer of two L-tyrosine units is favored in this reaction. Additionally, in the reaction to obtain **8**, a higher reactant concentration, 0.17 M of **4**, with formaldehyde was used compared with the reaction in which 0.040 M L-tyrosine was used to synthesize **3** in aqueous basic medium. The results show that the reaction of **4** with formaldehyde favors the formation of oligomers with a lower molecular weight. This behavior is most likely because **4** exists as an ion pair in solution, and the bulky tetrabutylammonium cation generates a steric hindrance, slowing the reaction of the L-tyrosine units with formaldehyde.

The reaction of **4** at a 0.12 M concentration with a reaction time of 3 days while maintaining the remaining conditions from the



Scheme 5. Reaction of tetrabutylammonium L-tyrosinate **4** with formaldehyde in acetonitrile.



Scheme 6. Proposed behavior of tetrabutylammonium L-tyrosinate **4** in acetonitrile.

previous reactions leads to product **6** as the primary product and **7** as a minor product (Scheme 5). Contrary to the reaction performed with L-tyrosine in aqueous basic medium, no signals assignable to **5** were observed because, in the reaction of **4** with formaldehyde, no base is added, which would improve the nucleophilic character of the phenol and favor another substitution in the *ortho* position to the phenolic hydroxyl.

The results of the study of the reaction of tetrabutylammonium L-tyrosinate **4** with two equivalents of formaldehyde in acetonitrile along with the results obtained for the reaction of L-tyrosine with formaldehyde in aqueous basic medium showed that the formation of linear oligomers of the general structure **6** is favored, and the formation of the azacyclophane **2** was not observed in any of the cases (Scheme 5). It is proposed that this behavior can be explained in terms of the pre-organization of the molecules in solution. The ESI-MS spectrum in the negative mode of **4** in CH_3CN (Fig. 2) showed the $[C_{34}H_{56}N_3O_6]^-$ ion at *m*/*z* 602.35 (calculated: 602.42), which is assignable to structure **9**, as shown in Figure 2.

The appearance of this species indicates that in dissolution, **4** is organized in ion pairs that associate with each other, forming linear arrangements stabilized by electrostatic interactions, thus minimizing steric repulsions (Scheme 6). The formation of linear arrangements between the molecules of **4** favors the condensation reaction toward linear products, and it is not possible to obtain the expected macrocyclization product.

In conclusion, it was established that in the reaction of L-tyrosine or its tetrabutylammonium salt with formaldehyde, no cyclophane-type macrocyclic compounds are formed, and it is only possible to obtain linear oligomers of two or more units of L-tyrosine bound by methylene groups.

The characterization of tetrabutylammonium L-tyrosinate **4**, which is a quaternary ammonium salt of L-tyrosine soluble in acetonitrile and dimethyl sulfoxide, is reported for the first time. The solubility of this compound in organic solvents allows its use in future reactivity studies of the amino acid L-tyrosine in solution because the amino acid presents low solubility in water and is insoluble in organic solvents.

Acknowledgments

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17. *Reaction of L-tyrosine with formaldehyde:* In a typical procedure, a mixture of L-tyrosine (x mmol) and NaOH (1 or 2 equiv) in water was stirred at room temperature. When a translucent solution was obtained, 37% formaldehyde was added (2 equiv or an excess greater than 10 equiv), and the resulting mixture was stirred at room temperature for a determined duration, after which it was neutralized with 2% HCl. The obtained precipitate was filtered, washed with distilled water and dried at 50 °C for its subsequent characterization by solubility, melting point, IR and NMR (^1H and ^{13}C) analyses. Using this method, products **5**, **6**, and **7** were obtained by varying certain reaction conditions.
*Product **5**:* Melting point: The product did not melt up to 400 °C. Product 5 darkened over the temperature range of 271–275 °C. FT-IR (KBr, cm^{-1}): 3193 (N—H), 3500–2500 (O—H), 1618 (C=O carboxylic acid). ^1H NMR (400 MHz, D_2O) δ 6.87–6.32 (m, 2H); 4.46–4.20 (m, 2H); 3.94–3.51 (m, 2H); 3.30–3.12 (m, 1H); 2.78–2.21 (m, 2H). Elemental analysis: calculated for $(C_{11}H_{13}NO_4)_n$ C 59.19; H 5.87; N 6.27; found C 56.46; H 5.91; N 5.87.
*Product **6**:* Melting point: The product did not melt up to 400 °C. FT-IR (KBr, cm^{-1}): 3384 (N—H), 3500–2500 (O—H), 1629 (C=O carboxylic acid). ^1H NMR (400 MHz, D_2O) δ 7.00 (d, J 7.9 Hz, 1H); 6.92 (s, 1H); 6.64 (d, J 8.2 Hz, 1H); 3.96 (d, J 13.4 Hz, 1H); 3.71 (d, J 13.2 Hz, 1H); 3.44 (d, J 6.4 Hz, 1H); 2.94 (dd, J 13.8; 5.2 Hz, 1H); 2.81 (dd, J 12.8; 6.6 Hz, 1H). Elemental analysis: calculated for $(C_{10}H_{11}NO_3)_n$ C 62.17; H 5.74; N 7.25; found C 59.26; H 5.97; N 7.02.
*Product **7**:* Melting point: 289–299 °C. R_f = 0.40 (Silica gel 60 H, 1-butanol: acetic acid–water 12:3:5). FT-IR (KBr, cm^{-1}): 3220 (N—H), 3500–2500 (O—H), 1616 (C=O carboxylic acid). ^1H NMR (400 MHz, D_2O) δ 7.02 (d, J 8.2 Hz, 2H); 6.99 (d, J 8.2 Hz, 2H); 6.90 (s, 2H); 6.65 (d, J 8.3 Hz, 2H); 6.61 (d, J 8.3 Hz, 2H); 3.92 (d, J 13.4 Hz, 2H); 3.70 (td, J 13.6; 4.2 Hz, 2H); 3.50–3.31 (m, 3H); 3.01–2.60 (m, 6H). ^{13}C NMR (100 MHz, D_2O) δ 181.2; 179.1; 178.9; 161.0; 158.7; 158.1; 130.5; 130.4; 130.0; 125.8; 125.0; 122.8; 122.7; 122.6; 117.6; 117.5; 117.3; 117.0; 64.0; 57.2; 48.8; 39.2; 37.2; 37.1. High Resolution Mass Spectrometry (HRMS) (ESI), *m*/*z* calculated for $[C_{29}H_{33}N_3O_9+H]^+$ 568.2290; found: 568.2286 $[M+H]^+$; 590.2067 $[M+Na]^+$; 566.2043 $[M-H]^-$.

18. *Synthesis of tetrabutylammonium L-tyrosinate (TyrONBu$_4$, **4**):* Tetrabutylammonium hydroxide (0.1 N, 0.8 equiv) was added dropwise to a suspension of L-tyrosine (3 mmol) in 40 mL acetonitrile cooled in an ice water bath. The mixture was stirred for 90 min, the solvent was removed at reduced pressure, and the obtained residue was redissolved in 40 mL acetonitrile. The mixture was filtered to remove the excess of L-tyrosine, and the filtrate was dried at reduced pressure, obtaining compound **4** as a cream colored hygroscopic solid (0.88 g, 98%), which was soluble in acetonitrile and dimethyl sulfoxide (DMSO). Melting point: 148–153 °C (melts with decomposition). FT-IR (KBr, cm^{-1}): 2962, 2875, 1593 (C=O carboxylate). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 8.4 Hz, 2H); 6.64 (d, J = 8.1 Hz, 2H); 3.15 (m, 8H); 2.97 (dd, J = 8.3; 2.6 Hz, 1H); 2.87 (dd, J = 13.3; 3.7 Hz, 1H); 2.30 (dd, J = 13.0; 9.5 Hz, 1H); 1.55 (m, 8H); 1.29 (h, J = 7.3 Hz, 8H); 0.92 (t, J = 7.3 Hz, 12H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.9; 156.2; 130.1; 129.9; 115.1; 79.3; 58.2; 57.6; 23.1; 19.2; 13.5. Elemental analysis: C 68.81; H 11.00; N 6.58 (calculated for $C_{25}H_{46}N_2O_3{\cdot}H_2O$ C 68.14; H 10.98; N 6.36). MS (ESI), m/z: 242.10 (calculated for $[C_{16}H_{36}N]^+$ 242.28); 179.75 (calculated for $[C_9H_{10}NO_3]^-$ 180.07).

19. *Reaction of tetrabutylammonium L-tyrosinate **4** with formaldehyde:* In a typical procedure, 37% formaldehyde (2 equiv) was added to a solution of tetrabutylammonium L-tyrosinate (**4**, x mmol) in acetonitrile, and the resulting mixture was stirred at room temperature for a determined duration, after which the solvent was removed at reduced pressure. The obtained residue was dissolved in distilled water and neutralized with 0.2 M HCl. The obtained precipitate was filtered, washed with distilled water, and dried at 50 °C for its subsequent characterization by solubility, melting point, IR and NMR (^{1}H and ^{13}C) analyses. Using this method, products **6** and **8** were obtained by varying certain reaction conditions.
*Product **8**:* Melting point: 265–270 °C. FT-IR (KBr, cm^{-1}): 3206 (N—H), 3500–2500 (O—H), 1607 (C=O carboxylic acid). MS (ESI), m/z calculated for $[C_{19}H_{22}N_2O_6\text{-}H]^-$ 373.14; found: 373.00 [M–H]$^-$.

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