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Synthesis and conformational analysis of azacyclophanes from L-tyrosine

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ABSTRACT

The synthesis of a new azacyclophane formed by two L-tyrosine units joined by two methylene bridges is presented. The structural and conformational characteristics are briefly discussed. Spectroscopic and theoretical data reveal a *syn* structure with two intramolecular hydrogen bonds.

Cyclophanes are macrocyclic compounds that contain two or more aromatic rings bonded in *meta* or *para* positions by small spacers. The molecular topology of cyclophanes determines their electronic and chemical properties.[1,2] The topology of cyclophanes can be synthetically modulated to achieve selective bindings to different chemical species. Among cyclophanes we find the azacyclophanes, which are an interesting group of synthetic receptors that combine the π-interaction capacity of cyclophanes with the acid–base properties of nitrogenated heterocycles; this combination of properties makes azacyclophanes good candidates for a wide range of applications in emerging technologies as synthetic receptors in molecular recognition, sensors, and components of molecular motors.[3–5]

The insertion of phenolic units into the cyclophane structure has a crucial impact on its reactivity and structure. For instance, previous studies have shown that phenol hydroxyl groups directed toward the macrocycle cavity increase cyclophane capacity to form complexes with metal cations and some organic compounds.[6] In addition, the formation of intramolecular hydrogen bonds between phenolic OH groups and other heteroatoms increase the rigidity and selectivity of these compounds.[7,8]

Recently, we reported a simple, inexpensive and highly efficient method to synthesize a new chiral *meta*-heterocyclophane. This heterocyclophane contained two 3,4-dihydro-2*H*-1,3-benzoxazine units joined by two ethylene bridges forming the (5*S*,14*S*)-5,14-diethoxycarbonyl-2,11-dioxa-4,13-diazapentacyclo[11.5.3.3.^{4,16}0.^{10,23}0.^{1,20}]tetracosa-1(18),7,9,16,20,23-hexaeno **1.** This compound was obtained in a one-step reaction of L-tyrosine ethyl ester with a large excess of formaldehyde in basic medium.[9]

In order to study the stability of heterocyclophane **1**, a sample of **1** was treated with HCl (10%) until complete dissolution. The resulting solution was neutralized with NH_4OH 25%. This experiment yielded a new tricyclic azacyclophane formed by two units of L-tyrosine joined by two methylene groups forming the (4*S*,13*S*)-4,13-dicarboxy-9,18-dihydroxy-3,13-diazatricyclo[1.^{1,15}-1.^{6,10}] cosa-1(18),6,8,10,16,19-hexaeno macrocycle **2**. In this Letter, we report the synthesis and structural characterization of this novel chiral azacyclophane (Scheme 1).

The new azacyclophane **2** was isolated as a brown amorphous solid, insoluble in common organic solvents, but soluble in aqueous solutions of inorganic acids and bases. The ESI-MS of sodium dicarboxylate of **2** gave a molecular ion at 430.3 (*m*/*z*), this being consistent with a $C_{20}H_{20}N_2Na_2O_6$ formula. The IR (KBr) spectrum of **2** presented bands at 3432, 3300–2300 (broad band), 1730 and 1620 cm^{-1}. The new structure was unambiguously determined by 1D (^1H, ^{13}C) and 2D (COSY, HMQC, HMBC, and NOESY) NMR. These spectroscopic data were also compared with the data reported for **1**. The ^1H NMR spectrum presented the characteristic signals of 1,2,4-trisubstituted rings in the aromatic region. The diastereotopic hydrogens were observed in the aliphatic region at 2.68 and 2.61 as multiplets. This overlapping of signals is produced by the two methylene groups present in the molecule. We also found other signals corresponding to the chiral methines at 3.56 and two N–CH_2–ph groups at 3.59 and 3.72 ppm. In a careful comparison of the ^1H NMR spectra of **1** and **2** we observed that neither ethyl ester nor N–CH_2–O group signals are present in the spectrum of **2** (Fig. 1).

The NOESY spectrum of **1** showed correlations that allow us to conclude: First, that the two units of benzoxazine are face to face, and second, that the hydrogen on the chiral carbon is in *pseudo*-axial position and as a result the ethyloxycarbonyl adopts a *pseudo*-equatorial position.[9]

Semi-empirical PM6 calculations were performed on **1** using MOPAC 2009.[12,13] The optimized structure of **1**, achieved at this level of theory correlates perfectly with the information obtained from the spectroscopic analysis. The optimized structure also shows that the oxazynic ring adopts a semichair conformation, where the nitrogen atom is pushed out of the benzene plane toward the cavity whereas the carbon between the oxygen and nitrogen on the oxazine ring is pulled out of benzene plane and away from the cavity (Fig. 2).

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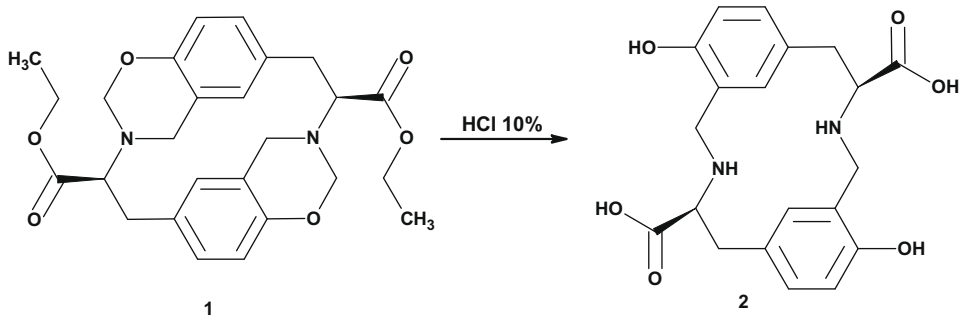


Scheme 1. Synthesis of the new azacyclophane **2**.

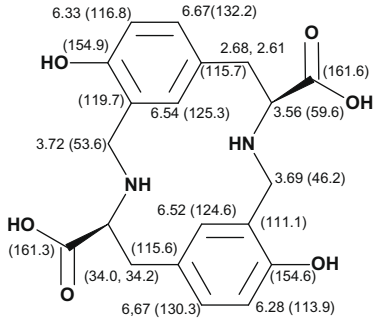


Figure 1. ^{1}H NMR (^{13}C) ppm spectroscopic data of **2** in D_2O.

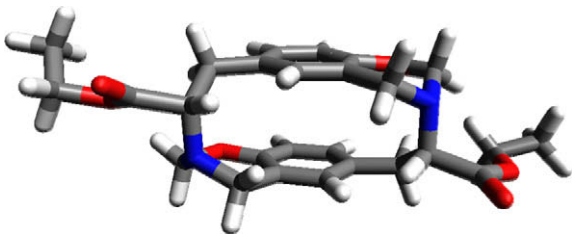


Figure 2. Optimized structure of **1**.

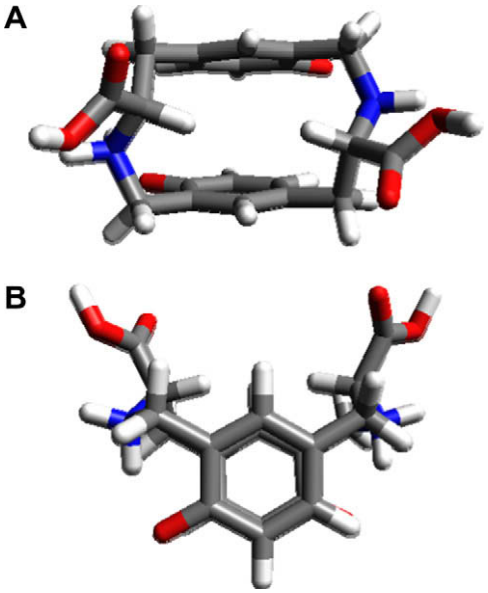


Figure 3. Optimized structure of **2**. (A) Front view, (B) side view.

The structure of compound **2** was also optimized at the PM6 level of theory. Our results show that the cavity size of **2** is similar to that of **1.** We also find that the aromatic rings adopt a face to face conformation which is a characteristic feature of *meta*-cyclophanes. As opposed to **1**, the hydrogens on the chiral carbons of **2** are in *pseudo*-equatorial position directed toward the interior of the macrocycle cavity. PM6-optimized structure also shows that the carboxyl groups adopt *pseudo*-axial positions giving the molecule a *syn* conformation (Fig. 3).[10,11]

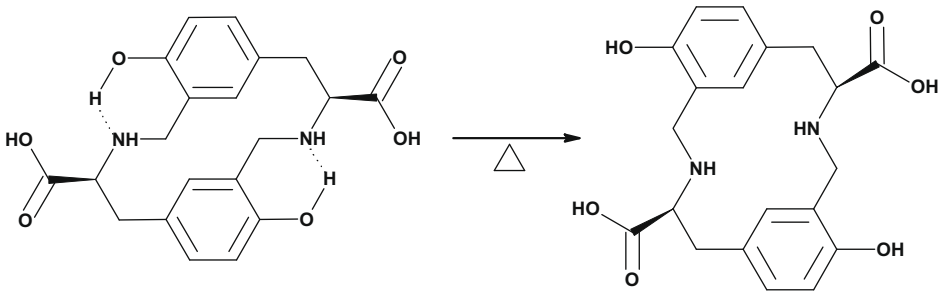
The optimized structure of **2** also reveals the existence of intramolecular hydrogen bonds (Scheme 2).

In order to explore the behavior of compound **2** in aqueous solution, we obtained ^{1}H NMR spectra of **2** at 25 °C and 60 °C (Fig. 4). A close comparison of the spectra at 25 °C (Fig. 4A) and 60 °C (Fig. 4B) shows that both spectra present the same number of signals. Nonetheless, there is an increase in the chemical shifts of the order of 0.3–0.5 ppm in all signals of the spectrum at 60 °C. We propose a possible explanation to these shifts: the intramolecular hydrogen bonds formed between N–H and O–H groups in the six-membered ring that are present in the PM6 calculations of **2** may exist in aqueous solution at 25 °C. The downfield shifts observed at a higher temperature may be due to the presence of an open form of **2** at 60 °C (Scheme 2). The broad absorption in the region 3300–2300 cm^{-1} of the IR spectrum is due to the OH-stretching vibration of the OH group in the intramolecular OH–N bond and confirms the presence of intramolecular hydrogen bonds.

From Figures 4A and B we find that compound **2** contains both hydrophobic and hydrophilic groups in its structure; as a consequence, it is very likely that **2** forms aggregate in aqueous solution. The downfield shifts seen at a higher temperature may be due to de-aggregation.

We have studied the temperature and concentration effects on the hydrogen bonding and aggregation. In order to study these effects we obtained a ^{1}H NMR spectrum of **2** at 25 C at a lower concentration (Fig. 4C). Figure 4C shows that there is an increase in the chemical shifts of around 0.1–0.2 ppm in all signals of the spectrum. This behavior, therefore, confirms that azacyclophane **2** forms aggregates in aqueous solution. Nonetheless, the formation of hydrogen bonds should not be rejected.

In conclusion, this work presents the synthesis of a new azacyclophane formed by two units of L-tyrosine joined by two methylene bridges. The structural analysis suggests a *syn* conformation with the hydrogens on the chiral carbons in *pseudo*-equatorial position directed toward the interior of the macrocycle cavity.



Scheme 2. Intramolecular hydrogen bonds of **2**.

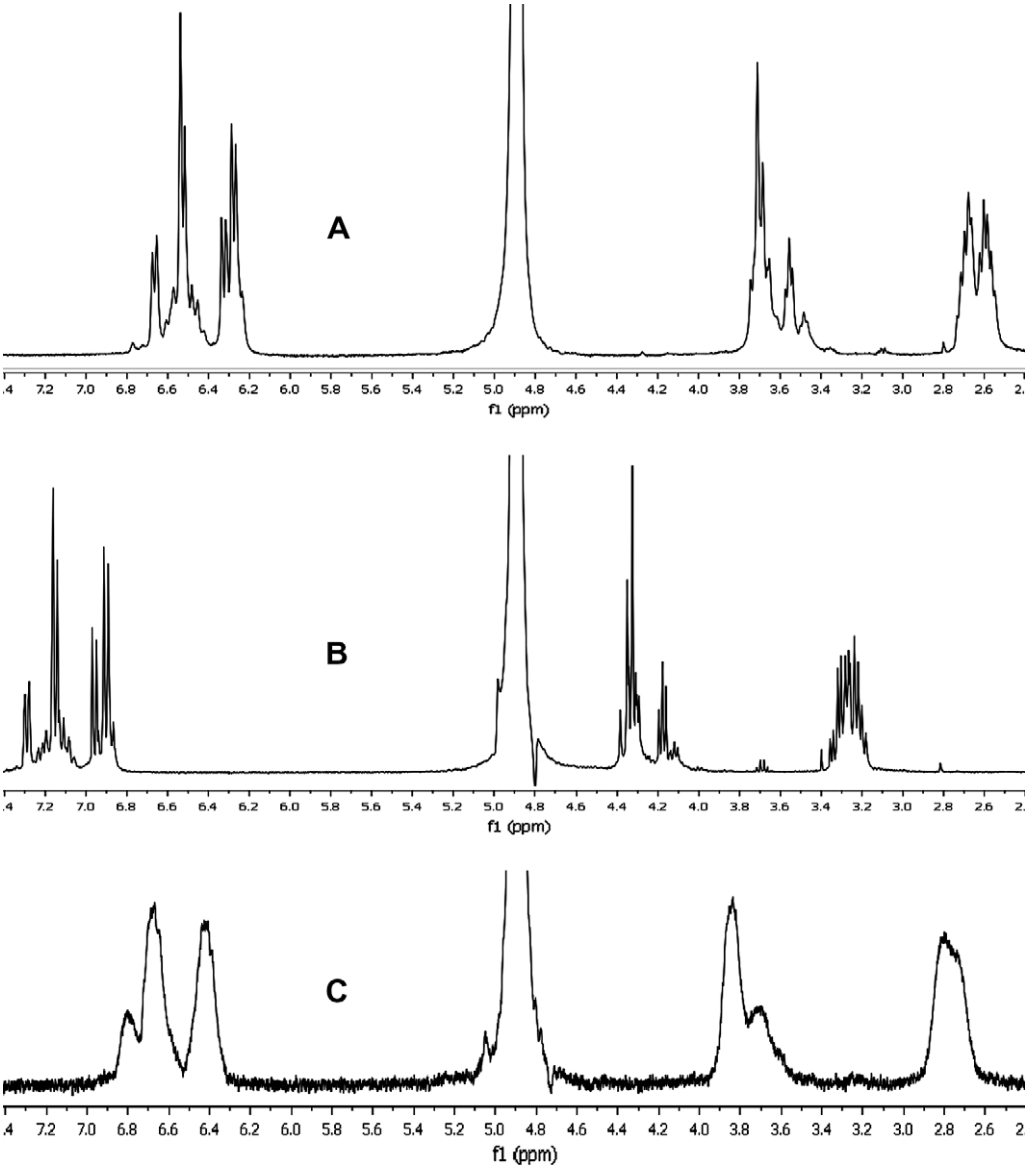


Figure 4. ^{1}H NMR of **2** in D_2O: (A) 25 °C (3 mg/0.5 mL), (B) 60 °C (3 mg/0.5 mL), (C) 25 °C (1 mg/0.5 mL).

*Procedure for azacyclophane **2** synthesis*: 0.5 g of compound **1** were stirred in 10 mL of HCl 10% until complete dissolution. The resulting mixture was treated with NH_3 25% until a precipitate appeared. The precipitate was filtered and washed with ethyl alcohol and subsequently dried, obtaining 0.39 g. Yield: 94%. Mp: no changes were observed when a sample was heated to 350 °C.

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