SYNTHESIS OF HIGHLY CHARGED C3-SYMMETRICAL ORGANIC MOLECULE WITH A FUSED PLANAR CORE STRUCTURE

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GRAPHICAL ABSTRACT

Abstract A new C3-symmetric molecule integrated with a number of interesting features, including three highly charged and flexible pyrrolidinium arms extending from a fused planar core structure, is synthesized.

Keywords C3-symmetric molecule; G-quadruplex ligand; heterocyclic compound; planar molecule

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INTRODUCTION

The synthesis of symmetric organic molecules is of great interest to molecular chemists. Molecular symmetry is a fundamental concept in chemistry as it helps predict or explain many of a molecule’s chemical properties such as dipole moment and molecular interaction behaviors. The principles of symmetry have successfully inspired and directed the design of molecules for many years.\(^1\) In particular, the twofold rotational symmetry has been engaged in various chiral ligands and catalysts.\(^2\) For this reason, there is ongoing interest in the exploration of \(C_3\)-symmetric molecules and ligands in areas of catalysis,\(^3\)–\(^5\) synthesis,\(^6\) molecular recognition,\(^7,8\) biomolecular interaction and stabilization,\(^9,10\) and materials science.\(^11\)–\(^14\)

In recent years, the design of planar organic molecules has been an important research topic, particularly for the investigation of biomolecular interactions.\(^15\) For example, searching for suitable molecular scaffolds as the stabilizing ligands or agents for DNA G-quadruplex (a drug target for anticancer therapy) has attracted growing attention because of the fact that stabilizing G-quadruplex structure in telomeric DNA is prone to inhibit the activity of telomerase and thus disrupt telomere capping and maintenance.\(^9,10\) Most G-quadruplex ligands show poor selectivity due to \(\pi\)-stacking interaction, which also occurs with common G-tetrads surface.\(^16\) The development of novel molecular geometries for stabilizing G-quadruplex is significant; however, methodology for the synthesis of water-soluble \(C_3\)-symmetrical molecules is limited. In this study, a new \(C_3\)-symmetric organic molecule with a fused planar core structure was synthesized. Key features such as three highly charged and flexible pyrrolidinium arms extending from a fused planar structure are integrated in the molecule. The compound with such a unique \(C_3\)-symmetrical molecular structure could be an attractive G-quadruplex ligand.

RESULTS AND DISCUSSION

The synthetic route to the target compound is depicted in Scheme 1. An intermediate of 3-bromopropylmethylpyrrolidinium bromide (1) was prepared in acetone with quantitative yields according to literature methods.\(^17,18\) The obtained compound was further reacted with imidazole in acetonitrile under refluxing conditions for 12 h to give 1-[3-(1H-imidazol-1-yl)propyl]-1-methylpyrrolidinium bromide (2) as a white solid with 95\% yields. For the synthesis of \(L(Br)(ClO_4)\)\(_3\), an ethanol solution of 2 and di-isopropylethylamine (DIEA) was added dropwise to a cyanuric chloride solution at 0 °C. The resulting solution was kept stirring for 30 min under the same conditions and then was heated to reflux for another 10 h. The reaction mixture after being cooled to room temperature, and acetone was added to precipitate out the products from the solution. The solids collected by filtration were washed with hot acetone and then dried in vacuo. The compound \(L(Br)\)\(_3(Cl)\)\(_3\) obtained is a highly hygroscopic salt most probably due to the bromide and chloride counterions.

An attempt was made to replace the anions by perchlorate \((\text{ClO}_4^-)\). \(L(Br)\)\(_3(\text{Cl})\)\(_3\) was redissolved in methanol. To this stirring solution, perchloric acid was added dropwise at room temperature. After 30 min, the solution was cooled to 0 °C. Cold acetone was added to precipitate the product out. The precipitate was collected by filtration and washed with iced water. The isolated solid was dried in vacuo to afford
Scheme 1. Synthetic route to $\text{L(Br)}_5\text{(ClO}_4)_5$. 

Figure 1. ESI-MS spectrum of $[\text{L(ClO}_4)_4\text{Br}]^+$. The inserted is a simulated spectrum (isotopic distribution graph) for the proposed species.
70% yields. In the beginning, the compound obtained was supposed to be \( \text{L(ClO}_4\text{)}_6 \) because perchloric acid solution was used largely in excess for anion exchange. However, the characterization results of the compound give unexpected findings. Electrospray ionization–mass spectrometry (ESI-MS) analysis, as shown in Fig. 1, clearly indicates that a bromide anion is observed in the MS signal of the compound, \( m/z = 1139.3 \) for \([\text{L(ClO}_4\text{)}_4\text{Br}]^+\). The experimental isotopic patterns are found perfectly matched with simulated spectrum (the isotopic distribution graph inserted in Fig. 1) for the proposed species. Interestingly, these results were persistently found even repeating the anion exchange with perchloric acid solution. This may imply that the highly charged ligand \( \text{L} \) has strong preference to bind with a \( \text{Br}^- \) and thus it did
not replace by ClO$_4^-$ as the Cl$^-$ did in the anion exchange process with perchloric acid solution. The chemical formula of the isolated compound is identified not as the predicted compound L(ClO$_4$)$_6$, but it is L(Br)(ClO$_4$)$_5$, which is further confirmed by elemental analysis of its CHNO contents.

The targeted C$_3$-symmetric organic molecule is designed to possess a fused planar core structure. In the molecule, the fused core is composed of three imidazolium units and a cyanuric ring at the 1, 3, and 5 positions respectively. Although the three C-N bonds which bridge the planar cyanuric core with three imidazolium units are rotatable, from the top and side of the three-dimensional (3D) model of L(Br)(ClO$_4$)$_5$, shown in Fig. 2, a coplanar orientation is observed for the four conjugated rings. This positively charged flat scaffold could be possibly beneficial for molecular interaction investigations such as DNA G-quadruplex through the charge effect and π-stacking interactions.

CONCLUSION

In conclusion, a new and highly charged C$_3$-symmetric molecule with a fused planar core structure was synthesized and characterized. The compound was found unexpectedly to chelate with a bromide anion that is not readily replaced by perchlorate, while its chloride ions are easily exchanged under the same conditions. The four conjugated rings composed by three imidazolium units and a cyanuric ring are found in coplanar orientation.

EXPERIMENTAL

**Synthesis of Intermediate 1**

The intermediate of 3-bromopropylmethylpyrrolidinium bromide (1) was prepared in quantitative yield according to a literature method.$^{[17,18]}$ $^1$H NMR (400 MHz D$_2$O): δ 2.14–2.25 (m, 4H), 2.30–2.41 (m, 2H), 3.08 (s, 3H), 3.51–3.62 (m, 8H).

**Synthesis of Intermediate 2**

The intermediate of 1-[3-(1H-imidazol-1-yl)propyl]-1-methylpyrrolidinium bromide (2) was prepared by the reaction of 1 (4 mmol, 1.0 g) and imidazole (12 mmol, 0.82 g) with DIEA (4 mmol, 0.66 mL) as the base in acetonitrile (10 mL) under refluxing conditions for 12 h. After reaction, cold acetone was added to the reaction mixture and the resulting organic solution was decanted. The oily residue was extracted several times with acetone to completely remove the starting materials. Compound 2 with 95% yield (1.1 g) was obtained as the white solid. $^1$H NMR (400 MHz D$_2$O): δ 2.17–2.38 (m, 4H), 2.39–2.46 (m, 2H), 3.08 (s, 3H), 3.38–3.80 (m, 8H), 9.17 [s, 2H (merged signal)], 9.53 (s, 1H); $^{13}$C NMR (400 MHz, D$_2$O): δ 24.73, 28.33, 47.28, 51.56, 64.56, 68.05, 142.46, 137.20, 138.81; ESI-MS m/z: 194, [M –Br$^-$]+, 274 [M$^+$].

**Synthesis of L(Br)(ClO$_4$)$_5$**

Cyanuric chloride solution (1.3 mmol, 0.24 g in 8 ml ethanol) was added dropwise to an ethanol solution (8 mL) of intermediate 2 (1.4 g, 5.1 mmol) and DIEA
(5 mmol, 0.8 mL) at 0 °C. The resulting solution was kept stirring for 30 min at 0 °C and then heated to reflux for 10 h. The reaction mixture was cooled to room temperature, and acetone was added to precipitate the crude products. The solvents were decanted, and the residue was washed with hot acetone. The dried solids were redissolved in 5 mL methanol. Perchloric acid solution (30 mmol in 5 mL methanol) was added dropwise to the solution and the resulting solution was kept stirring. After 30 min at room temperature, the solution was then cooled to 0 °C and cold acetone was added to precipitate the products. The precipitate was collected by filtration, washed with ice water, and then air dried. L(Br)(ClO₄)₅ was isolated as the white solid with 70% yield (1.1 g). ¹H NMR (400 MHz D₂O, broad signal): δ 2.23 [m, 12H (merged as one broad signal)], 2.39–2.60 (m, 6H), 3.05–3.20 (m, 9H), 3.41–3.57 (m, 18H), 4.29–4.38 (m, 6H), 7.33 (s, 3H), 7.45 (s, 3H), 8.35 (s, 3H); ¹³C NMR (400 MHz, D₂O): δ 24.82, 28.14, 48.45, 51.80, 64.39, 68.42, 119.87, 124.68, 126.31, 127.65; ESI-MS m/z: 519.2 [L(ClO₄)₃Br]⁺, 1139.3 [L(ClO₄)₄Br]⁺. Elemental analysis: anal. calcd. for [L(ClO₄)₅Br · 4H₂O] (%): C, 33.00; H, 5.23; N, 12.83; O, 29.30. Found (%): C, 33.01; H, 5.32; N, 12.80; O, 29.33.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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