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Synthesis and Computational Evaluation of a Boronium Ion Analogue of the Tropane Ring System

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Abstract: Reaction of bromoborane-dimethylsulfide with homopiperazine results in direct formation of a boronium ion analog of the tropane ring system. Calculations at the DFT/6-31G* level confirm the structural similarity of the two systems, and provide insight into the stability of the boronium ion in aqueous solutions.

For boronium ions of composition $[R_2BL_2]^+$, where L = amine, there exists an isosteric relationship between the boronium [N-BR_2-N] unit and the [C-NR_2-C] unit present in secondary (R=H) ammonium ions.[1] Given the widespread interest in the preparation of isosteres of biologically significant functional groups, we deemed it worthwhile to prepare a boronium-ion analogue of a known "biostructural" element and to computationally compare the two species.

The 8-azabicyclo[3.2.1]octane ring is a central structural element in a number of neuroactive compounds, including cocaine and atropine.[2] We have prepared a boronium-ion analog (**2**, Figure 1) of the conjugate acid of 8-azabicyclo[3.2.1]octane (**1**) in a one-step, one-pot procedure. The preparation of the bromide salt of **2** is exceedingly simple, the product precipitating as a white solid upon combining equimolar quantities of homopiperazine and bromoborane-dimethylsulfide in CH_2Cl_2. The proposed product formulation is supported by elemental analysis, and the assigned structure is consistent with the ^{1}H-, ^{13}C- and ^{11}B-NMR spectra of the compound.[3]

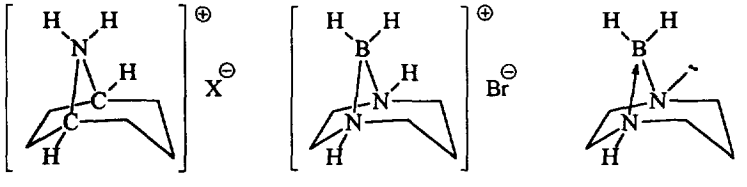

Figure 1. (*l to r*) Structure of **1**, and proposed structures of compounds **2** and **3**.

Like other boronium ions, compound **2** is stable in air and soluble in water and organic solvents such as acetone and alcohols. In CD_3OD or D_2O, the N-H protons exchange with deuterium, consistent with the formation of a putative intermediate, **3**, the conjugate base of **2**. When dissolved in water, **2** is stable for days (^{11}B-NMR), and may be conveniently recrystallized from water or alcohols by cooling warm, concentrated solutions. In order to determine the degree of structural similarity between **1b** and **2**, and to probe the nature of compound **3**, we undertook to model these species computationally.

The fully optimized, computed (DFT/6-31G*) structures of **1b** and **2** are remarkably similar in most respects (Figure 2).[4] The greatest differences between the compounds are the longer bridgehead bond lengths in **2** versus **1b** (B-N: 1.624 Å; C-N: 1.556Å) and the diminished bridgehead bond angle in the former (NBN: 94.11°; CNC: 107.65°). The B-N bond lengths in **2** fall between those known for B-N dative bonds and those of B-N covalent bonds with no added π component.[5] While the structures of the compounds are essentially superimposable, there are major differences in charge distribution between **1b** and **2**. In **1b**, the positive charge is located at the "top" of the molecule, on the N-bonded H atoms. In compound **2**, the positve charge is along the "sides" of the molecule, again on the N-bonded H atoms. The hydrogens on boron in **2** are slightly (-0.05) hydridic.

The decomposition of boronium ions containing secondary amine ligands may proceed through planar, three-coordinate intermediate $R_2B{=}NR_2$ species, arising from deprotonation of one amine accompanied by loss

of the second and formation of a double bond between boron and the remaining nitrogen center.[6] In this light, the computed structure of compound **3** is revealing. This structure displays an asymmetric N-B-N bridge, with one covalent and one dative B-N bond. It is notable that both nitrogens remain bonded to boron, that pyramidalization at the covalently-bonded nitrogen persists and that the boron remains tetrahedral. The deprotonated nitrogen atom is found to be the most negatively charged (-0.5) site within the structure, consistent with it being the site of reprotonation (deuteration) in protic solvents, reforming **2**. We speculate that the retention of the dative bond to one amine center and the lack of formation of a $\sigma,p\pi \Rightarrow p\pi$ double bond between boron and the second nitrogen may be responsible for the stability of compound **2** in water, and may be the consequence of the incorporation of the boronium ion at the bridgehead position in the structure. To our knowledge, **2** is only the second bicyclic boronium ion to be reported.[7]

Efforts to develop more elaborate, boronium-based isosteres of biologically significant structures are planned, as are efforts to develop isosteres derived from related boron-containing species (e.g., pyrazaboles).

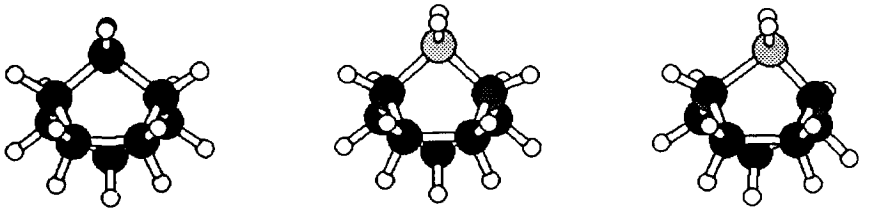

Figure 2. Optimized structures of compounds **1**, **2** and **3** (*l to r*). Black spheres = C; White spheres = H; Dark shaded spheres = N; Light shaded spheres = B.

Acknowledgements

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