

S0040-4039(96)00372-3

## 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.

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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.<sup>1</sup> 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.<sup>2</sup> 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  $^1H$ -,  $^{13}C$ - and  $^{11}B$ -NMR spectra of the compound.<sup>3</sup>

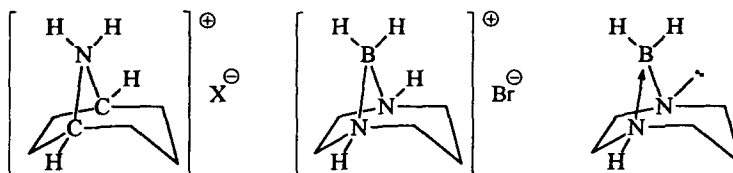


Figure 1. (l to r) Structure of **1**, and proposed structures of compounds **2** and **3**.

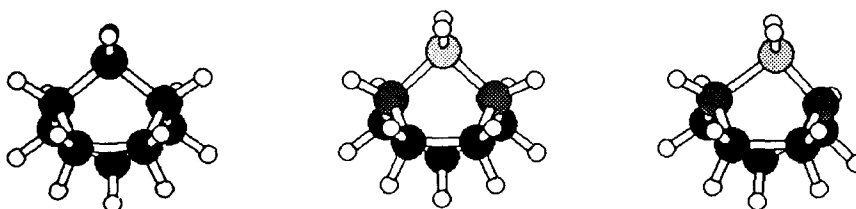
Like other boronium ions, compound **2** is stable in air and soluble in water and organic solvents such as acetone and alcohols. In  $CD_3OD$  or  $D_2O$ , the N-H protons exchange with deuterium, consistent with the formation of a putative intermediate, **3**, the conjugate base of **2**. When dissolved 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).<sup>4</sup> The greatest differences between the compounds are the longer bridgehead bond lengths in **2** versus **1b** (B-N: 1.624 Å; C-N: 1.556 Å) 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  $\pi$  component.<sup>5</sup> 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 positive 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.<sup>6</sup> 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  $\sigma, \pi \Rightarrow \pi \pi$  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.<sup>7</sup>

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

We are grateful for financial support of this work from Research Corporation (Grant No. C-3121), NSF/EPSCoR (Grant No. EHR-9108761) and the University of South Alabama.

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(Received in USA 30 January 1996; revised 13 February 1996; accepted 14 February 1996)