Ionic N–B–N- and B–N–B-Substituted Benzene Analogues: A Theoretical Analysis

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Supporting Information

ABSTRACT: Calculations are presented on six-\(\pi\)-electron N–B–N- and B–N–B-substituted benzene rings, \([\text{C}_3\text{BN}_2\text{H}_6]^+\) and \([\text{C}_3\text{NB}_2\text{H}_6]^−\), and their isomers. These compounds display a wide range of thermodynamic stability in those molecules, with N–B–N connectivity favored strongly in the cation, B–N–B in the anion. That stability order is easily understood using the charge distribution in a benzene polarized by heteroatom substitutions or the underlying allyl anion and cation. Deprotonation at N in \([\text{C}_3\text{BN}_2\text{H}_6]^+\) leads to a set of BN-substituted pyridines. The calculations predicted three B–N-substituted pyridines clearly more stable thermodynamically than those synthesized so far. The order of stability of the B–N–B-substituted benzenoid systems, which are as yet not well known experimentally, shows similar features. We investigated in a preliminary way the reactivity and potential stabilization by substitution of the energetically most stable structures and by examining possible escape routes by dimerization. Our study suggests new N–B–N and B–N–B molecules that could be made.

INTRODUCTION

Boron, nitrogen substitutions in benzene and other cyclic hydrocarbons have been an active and productive field of study for more than 50 years.1 With applications in pharmacology,2 electronic materials,3 and nanoscience,4 many B,N-containing organic compounds have been synthesized and studied theoretically.5–7 Their utility stems from the fact that B–N is isoelectronic to C–C. This makes it possible to prepare systems that are similar in structure to known hydrocarbons, but with different, tunable chemical reactivity and physical properties. In this paper, we look at two such B,N-substituted systems from a theoretical point of view.

Our study was motivated initially by a report of a preparation of diazaborines of the kind shown in structure 1.8

One N–B–N fragment of molecule 1 is extracted in 2; this is N\(_2\)BH\(_5\), isoelectronic to an allyl anion, \([\text{C}_3\text{H}_5]^−\). Like allyl anion, N\(_2\)BH\(_5\) has four \(\pi\)-electrons. We imagined a hypothetical condensation of structure 2 with allyl cation, \([\text{C}_3\text{H}_5]^+\), in a six-membered ring. The resulting molecule is cation 3, \([\text{C}_3\text{BN}_2\text{H}_6]^+\), isoelectronic to benzene.9,10

Analogously, one could think of constructing another molecule that is isoelectronic to benzene, using a B–N–B-\(\pi\) system with two \(\pi\)-electrons, NB\(_2\)H\(_5\). 4 is isoelectronic to allyl cation. Such B–N–B systems are less common than N–B–N ones, but a few are known.11,12 A condensation of 4, now with an allyl anion, leads to anionic structure 5, \([\text{C}_3\text{B}_2\text{NH}_6]^−\) also isoelectronic with benzene. In this paper, we study the chemical bonding and the stability of these hypothetical molecules, and their isomers and derivatives. We also study deprotonated isomers of 3 and their derivatives, in order to compare their stabilities with, as we shall see, known systems.

COMPUTATIONAL METHODOLOGY

All the structures we have studied were calculated in the framework of density functional theory (DFT). Becke’s three-parameter hybrid functional as modified by Lee, Yang, and Parr (B3LYP), and the split-valence 6-31+G (\(d,p\)) basis set was used, as implemented in the Gaussian 09 program.13 Harmonic vibration frequencies were calculated for all structures at the same level (B3LYP/6-31+G(d,p)//B3LYP/6-31+G(d,p)); all the molecules reported were found to be minima on
their potential energy surface. The electronic energies are corrected for the zero-point energies.

**RESULTS AND DISCUSSION**

\[\text{[C}_3\text{BN}_2\text{H}_6]^+.\] There are a number of possible positional isomers of \([3,6−10.14]\) These isomers are shown in Table 1, along with their calculated energies. Although not all isomers are known experimentally, derivatives of \([3,6,2,19]\) and \([7.15]\) were synthesized and crystallographically characterized.

Table 1. Structures 3, 6−10 and Their Relative Energies

<table>
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<th>Structure #</th>
<th>Structure</th>
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Among the isomers, 3 is calculated to have by far the lowest energy. Despite the high thermodynamic stability of 3, it is its other isomers that have received greater attention. So, derivatives of 6 (calculated to be 53 kcal/mol less stable than 3) have been prepared experimentally.\(^2\) We will return to a detailed consideration of these compounds below. Structure 3 has N−B−N connectivity of the heteroatoms, while the much less stable 6 contains B−N−N.

Let us first see what clues to the stability and aromaticity of the various species are to be found in the calculated equilibrium bond lengths of the molecules. Figure 1 shows the calculated bond lengths of 3 and 6 and, as references, benzene, borazine, allyl cation, 2, and the BN\(_2\)H\(_5\) models 11a,b. 11a is the optimized H\(_2\)BNHNH\(_2\) geometry, nonplanar and to be discussed in the next section. 11b is a planar, higher energy conformation of 11a, more suitable for comparison with the benzenoid structures.

Equalization of bond lengths is one criterion of aromaticity, and (perhaps) an indicator of stability.\(^20\) The calculated bond lengths in 3 are reasonably equalized, and consistent with models of 2, borazine, and allyl cation. For the less stable 6, the calculated bond lengths appear to be contradictory in the information they give us. On one hand, the bond lengths in the B−N−N segment of 6 are very different from the ones in a B−N−N model 11a,b. So the mixing with allyl cation segment has a large effect. On the other hand, we see signs of destabilization in the unequal C−C distances of 1.372 and 1.420 Å in 6 (or is it just inherent asymmetry?), and the very long B−C distance of 1.536 Å.

**Order of Stability of the [C\(_3\)BN\(_2\)H\(_6\)]\(^+\) Isomers.** In seeking an explanation of the great difference in stability of 3 and 6, we thought to go back to the positional isomer of BN\(_2\)H\(_5\) 2, namely 11. 11, however, has a degree of structural complexity, in that it prefers to be nonplanar, 11a, by about 9 kcal/mol relative to the planar conformation 11b. As Table 2 shows, both 11a and 11b are very high in energy above 2. The rotation of the terminal NH\(_2\) out of plane and its pyramidalization are indicative of a tendency for the lone pairs (full on terminal NH\(_2\), partial on the central N) to get out of each other’s way as they do in, for example, hydrazine.

The order of stability of 2 and 11 can be understood by analyzing the charge distribution in allyl anion, isoelectronic to the BN\(_2\)H\(_5\) models. The charge distribution of allyl anion, using the natural bond orbital (NBO) analysis (on wave functions calculated with the B3LYP 6-31+G(d,p) method), is shown in 12.

As expected from the four-\(\pi\)-electron system, the negative charge is highly localized on the two carbon atoms at the ends of the molecule. If we were to make a substitution (e.g., B,N) in allyl anion, placing the more electronegative atoms in the positions where there are most electrons (the outer atoms) should be favored.\(^2\) The less electronegative atoms should go into the site of less electron density. The N−B−N substitution fits the predicted pattern best, B−N−N less so. The calculated energetics of the various \([\text{C}_3\text{BN}_2\text{H}_6]^+\) isomers in Table 1 are reasonably consistent with this analysis.

**Table 2. Structures 2, 11a, and 11b and Their Relative Energies**

<table>
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<th>Structure #</th>
<th>Structure</th>
<th>E (kcal/mole)</th>
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</tr>
<tr>
<td>11a</td>
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<tr>
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<td>H(_2)B</td>
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Figure 1. Calculated bond lengths (in Å) of 3 and 6 and, as references, benzene, borazine, allyl cation, and the BN\(_2\)H\(_5\) models.
There is another way to approach the observed order of stability in 3 vs 6. The electron density in benzene is equally distributed between the carbon atoms. However, if we were to polarize benzene by substituting a single heteroatom, the charge distribution would change, and the resulting polarization would indicate where subsequent substituent would prefer to go. We take the case of a B-substituted benzene ([BC₅H₆⁺]) as one starting point for our analysis.

13 shows the charge distribution in the anionic ring, isolectronic to benzene. Positions 2 and 6 have the highest electron density, making them the most favored positions for substitution by high electronegative atoms. Positions 3 and 5 are less negative. Therefore, nitrogen atoms would favor positions 2, 4, and 6. This is consistent with the energy order found in Table 1. For example, structure 9, which has nitrogens substituted in positions 3 and 5, is less stable than 3 by about 59 kcal/mol.

Alternatively, one could begin with a N-substituted benzene (the pyridinium cation, [C₅NH₆⁺]). We then find electron deficiency at the ortho and para positions (2, 4, and 6), now favoring B substitution there.

In summary, arguments based on either the inherent charge asymmetry in the allyl anion or the polarization caused in an N- or B-substituted benzene ring, explain the calculated preference for N–B–N over B–N–B connectivity in the molecules under consideration. There are signs of destabilizing lone pair–lone pair repulsion in the B–N–N isomers.

Functionalization of Deprotonated 3 and 6. Most of the experimentally known derivatives of our molecules are based not on the parent cationic system, but a formally deprotonated [C₅BN₂H₆]−, i.e., C₅BN₂H₅. As Figure 2 shows, such molecules are neutral B,N-substituted pyridines with a B–N–N topology. These molecules were found to inhibit the synthesis of lipopolysaccharides in Gram-negative bacteria. We then calculate the pairs 16 and 17, 18 and 19, 20 and 21. In all cases the molecules with N–B–N connectivity are more than 20 kcal/mol more stable than the ones with B–N–N.

We also constructed structures isomeric to those shown in Table 3, now derived from deprotonated 7 and 8. Surprisingly, these were calculated to be more stable than 6 as well as being more stable than the experimentally known pharmaceutically active molecules. For instance, structure 22, shown below, was calculated to be more stable than its isomeric structure with N–B–N connectivity by 1 kcal/mol. When additional functional groups were added to 22 (guided by the known pyridine substitutions) to construct, for example, the isomeric structure of 18, the initial stability order was restored (derivatives of 14 most stable); 18 is now more stable by about 5 kcal/mol.

It is fascinating that generally the less stable (thermodynamically) isomers are those that are known and pharmacologically active. It could be that their very instability makes them kinetically more reactive at some enzyme active sites. The mechanism of the diazaborine inhibiting process and the kinetic stability of these molecules is beyond the scope of this study. We think it would be worthwhile, however, to synthesize the B–N-substituted pyridines 14, 16, 18, 20, and their isomers, derivatives of 7 and 8, predicted, in some cases clearly so, as the more stable isomers. And for the cases where isomeric structures are known, it would be important to have experimental measures of their relative stability to test our theoretical predictions.

It is interesting that one can generate neutral analogues of 3 and 5 by fusing a naphthalene unit to the three carbons of the six-membered ring. 3 and 5 then become B–N derivatives of a phenalenium cation and anion respectively. In fact, two of the known compounds, Figure 3, are of this type.

Isomers of [C₅B₂NH₄⁺]. In the second part of this paper, we consider the anionic benzene analogue [C₅B₂NH₄⁺], formed conceptually by a condensation of allyl anion, [C₅H₅⁻]−, with NB₃H₄, 4, in a six-membered ring. All possible positional isomers,

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**Table 3. Structures 14–21 and Their Relative Energies**

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<td><img src="image9" alt="Structure 22" /></td>
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**Figure 2.** Generic structures of the biologically active diazaborines. (Adapted from ref 2a.)
23−27, are drawn in Table 4 along with their relative energies. Now the B−N−B connectivity emerges as the most stable. To the best of our knowledge, no such B−N−B systems are known; in general, B−N−B systems are not common, and have not received much attention.11,12

Following an analysis similar to that in the first part of our paper, we compare 5 and 23 with various model systems in Figure 4.

Figure 4 shows the calculated bond lengths of 5 and 23 and, as references, benzene, borazine, allyl anion, and the NB2H5 models. 28a is the optimized H2NBHBH2 geometry, nonplanar. 28b is a planar, rotated 90° with respect to the molecular plane, higher energy conformation of 28a, for comparison with 4 and 5.

The calculated bond lengths in 5 are reasonably equalized, and consistent with models of 4, borazine, and allyl anion. On the other hand, signs of destabilization are clear in 23, in that the C−C bonds are very different from the ones found in allyl anion, and that the N−B bond length does not follow that of N−B−B model 28a,b. In examining the energetics of the model systems, 4 (planar) emerges as 30 kcal/mol below the optimum structure of its NBB isomer 28a (nonplanar), while a planar 28b is 4 kcal/mol higher.

Allyl cation, isoelectronic to the NB2H5 models, has the NBO charge distribution shown in 29. As expected for the two-π-electron system, the electron density peaks on the middle atom. If one were to make a substitution in allyl cation, the most electronegative atom(s) should go in the middle; the B−N−B substitution fits the predicted pattern best, N−B−B less so.

Proceeding to the other way we have found of explaining substitution, if we polarize benzene by substituting a nitrogen atom, we can predict which sites favor boron substitution by analyzing the electron density distribution of the substituted ring. 30 shows the charge distribution of cationic ring [NC3H3]+, isoelectronic to benzene. Positions 2 and 6 have the lowest
electron density, making them the most favored positions for substitution by less electronegative atoms. This is consistent with the energy order of the $[\text{C}_3\text{B}_2\text{N}_6\text{H}_6]^-$ isomers calculated. Analogous conclusions are reached if one begins with a B-substituted benzene (shown in 13 above).

Again, arguments based on either the inherent charge asymmetry in the allyl cation, or on the polarization caused by a heteroatom in a N- or B-substituted benzene ring explain the calculated preference for B–N–B over N–B–B connectivity in their molecules.

**Strategies for Stabilizing 3 and 5.** We have seen that among their isomers, 3 and 5 are quite stable. But could one stabilize these ions further by substitution?

It is difficult to come up with a quantitative measure of stabilization. We think we can find one in characteristic acid and base reactions of these molecules. For the cations we will look at the heat of hydride addition reaction

\[
\text{C}_3\text{N}_2\text{BH}_6^+ + \text{H}^- \rightarrow \text{C}_3\text{N}_2\text{BH}_7
\]

and compare that heat for a substituted and unsubstituted molecule. For the anion we will examine a corresponding protonation,

\[
\text{C}_3\text{B}_2\text{N}_6^- + \text{H}^+ \rightarrow \text{C}_3\text{B}_2\text{NH}_7
\]

31 shows the charge distribution in cation 3. Positions 3 and 5 on the allyl segment have low electron density. This is a consequence of the proximity of these to N atoms, and the memory of the polarization of the π-system of an allyl cation. Substituting a π-electron donor group for the hydrogen at one (or both) of these positions should have a stabilizing effect on the molecule. An NH$_2^-$ serves us as potential stabilizing substituent; our model is 32, which has NH$_2^-$ groups substituted at positions 3 and 5.

There are several possible positions for attack by H$^-$; we considered the ones that result in the most stable molecules, 33 and 34. The hypothetical reactions that were used to generate 33 and 34 are shown in Figure 5, along with their calculated heats of reaction. Since hydride addition to 32 is much less exothermic than that of 3, we reason that electron donor substitution had a stabilizing effect on 3. The assumption here is that the NH$_2^-$ substituent in 34 has little effect on the stability of the π-system remaining.

The charge distribution in anion 5, shown in 35, suggests π-acceptor substitutions at positions 3 and 5 for stabilization. 36 models this, with −CN groups as acceptors. Protonation of anions 5 and 36 would result in neutral molecules as shown in

Figure 6, along with the corresponding heats of reaction. The lower heat of protonation of 36 is indicative of stabilization, again under the assumption of little effect of the remaining cyanide substituent on the π-systems.

There are several possible positions for attack by H$^-$; we considered the ones that result in the most stable molecules, 33 and 34. The hypothetical reactions that were used to generate 33 and 34 are shown in Figure 5, along with their calculated heats of reaction. Since hydride addition to 32 is much less exothermic than that of 3, we reason that electron donor substitution had a stabilizing effect on 3. The assumption here is that the NH$_2^-$ substituent in 34 has little effect on the stability of the π-system remaining.

Figure 6, along with the corresponding heats of reaction. The lower heat of protonation of 36 is indicative of stabilization, again under the assumption of little effect of the remaining cyanide substituent on the π-systems.

Note that the two heats of reaction, for H$^+$ and H$^-$ addition, are very negative. This is because they are ionic recombinations; were solvents included in the calculations, the heats of reaction would be much reduced.

**Dimerization Escape Routes for 3 and 5.** In order to assess the stability of 3 and 5 further, we studied one escape route, dimerization. While these rings partake of some of the features of aromaticity, the boron atoms retain their π-acceptor character, through their only partially filled p-orbital. The N atom’s π-type lone pair is only partially depleted by delocalization. Thus, one would expect B–N bond formation to feature in hypothetical dimerization, as indicated by structures 37–39. Such a dimerization has been postulated in the literature for a B–N–B system.12 As Table 5 shows, such dimerizations are computed to be highly endothermic.

Before we use these large endothermicities as a proof of stability of the monomers, we need to consider whether the...
charge repulsion in 37 and 38 could be the reason behind the instability of the dimers. So we also looked at the neutral dimer, 39, isoelectronic to 37 and 38, resulting from substituting two carbon atoms by boron or nitrogen in 37 and 38, respectively. The heat of dimerization of 39 is calculated to be much less than that of the previous dimers, but is still positive. Thus, while Coulomb forces are clearly at work, these results point to a thermodynamic factor working against dimerization.

CONCLUSION

The stabilities of the six-$\pi$-electron cationic $[\text{C}_6\text{BN}_2\text{H}_6]^+$ and anionic $[\text{C}_6\text{BN}_2\text{H}_6]^-$ systems were investigated theoretically. Among all the studied structures of $[\text{C}_6\text{BN}_2\text{H}_6]^+$, $\text{N}^-$--$\text{N}$--$\text{N}$ connectivity corresponded to the most stable configuration. Based on the bond equalization criterion, such $\text{N}^-$--$\text{N}$--$\text{N}$ systems could be said to be aromatic. Extending our calculations to the Coulomb forces are clearly at work, these results point to a thermodynamic factor working against dimerization.

Table 5. Structures 37–39 along with Their Heats of Dimerization

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REFERENCES

(10) In our representations, we show the hydrogens on boron or nitrogen, but not at carbons. The reason for that will become clear as we discuss molecules that are dehydrogenated at N relative to those drawn here.
(14) The + sign inside the rings signifying formal aromaticity is not conventional, but serves as a reminder that these molecules are cations.

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12257
(21) This follows from a standard perturbation theory argument.