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Computational Studies on the Reactivity of Substituted 1,2-Dihydro-1,2-azaborines

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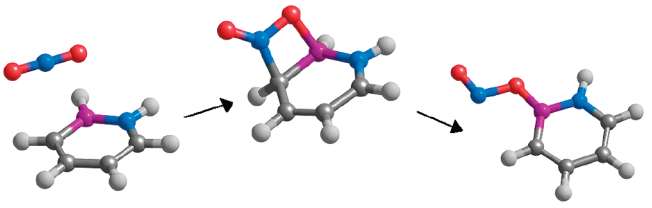

We have investigated important intermediates of electrophilic aromatic substitution reactions and one-electron oxidation of substituted 1,2-dihydro-1,2-azaborines with density-functional theory. The results show that electrophilic substitution reactions and one-electron oxidation of substituted 1,2-azaborines are generally much more favorable than those of the corresponding benzene derivatives. Both chlorination and nitration of several boron-unsubstituted 1,2-azaborines are expected to break the boron−hydrogen bond, yielding boron-chlorinated 1,2-azaborines and a novel class of boron-bound 1,2-azaborinyl nitrites, respectively. Comparison between the relative stabilities of C_3-bound and C_5-bound Wheland intermediates of different electrophilic substitution reactions of 1,2-azaborines further suggests that the preference of the C_3- over C_5-substitution decreases with decreasing electrophilicity of the attacking group.

I. Introduction

1,2-dihydro-1,2-azaborine (Scheme 1, henceforth abbreviated as 1,2-azaborine) is isosteric and isoelectronic with the ubiquitous benzene ring. Several syntheses of substituted 1,2-azaborines have been described since the 1960s,[1,2] but the chemistry of these compounds remained largely unexplored until the development (during the past decade) of new synthetic strategies[3−6] which allow the functionalization of the 1,2-azaborine ring with a large array of substituents. The similarity of this class of compounds with the arenes has recently been furthered through reports that 1,2-azaborines possess delocalized structures consistent with aromaticity.[7] Substituted 1,2-azaborines have recently been shown to be highly nucleophilic species: they readily undergo electrophilic aromatic substitution[6] on the 3- or 5-positions, depending on the specific reaction conditions. In late 2008, the preparation and spectroscopical characterization of the long-sought unsubstituted 1,2-dihydro-1,2-azaborine was achieved.[8] The continuing development of the chemistry of 1,2-azaborines is expected to allow the syntheses of boron-containing isosteres of pharmacological agents and conjugated organic materials.

To explore the reactivity of this interesting class of compounds, we have investigated important intermediates of electrophilic aromatic substitution reactions (nitration, halogenation, and acylation) and one-electron oxidation through density functional computations. The results show that electrophilic substitution reactions and one-electron oxidation of substituted 1,2-azaborines are generally much more favorable than that of the corresponding benzene derivatives. Both chlorination and nitration of several B-unsubstituted 1,2-azaborines are expected to break the B−H bond, yielding B-chlorinated 1,2-azaborines and a novel class of B-bound nitrite 1,2-azaborines, respectively.

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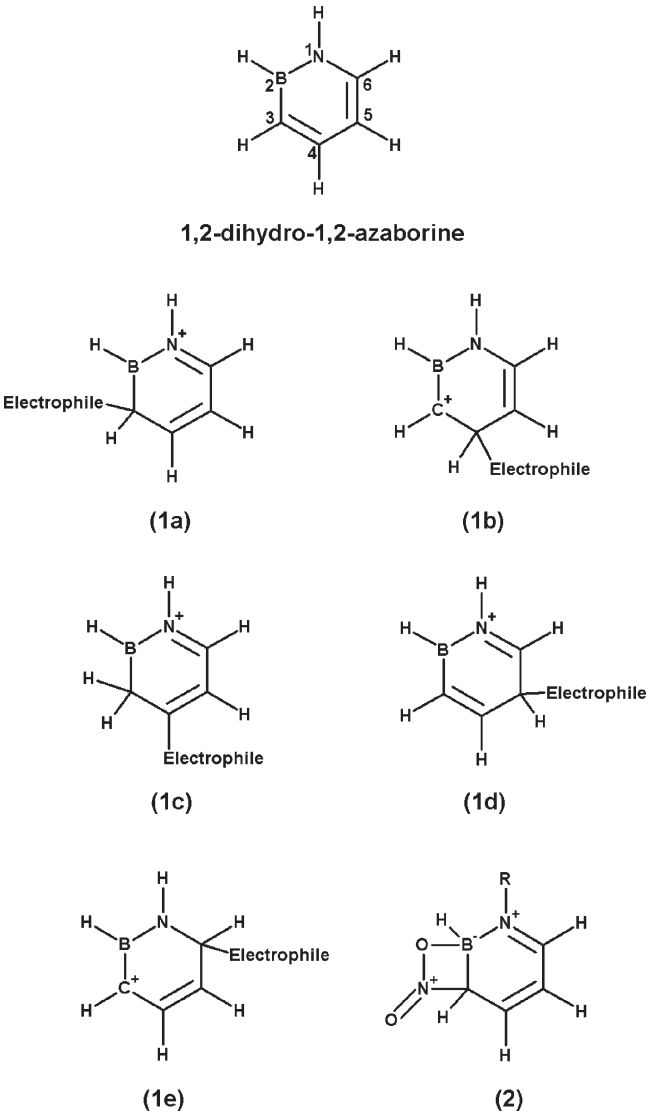
SCHEME 1. 1,2-Dihydro-1,2-azaborine and Important Intermediates in Its Electrophilic Aromatic Substitutions



II. Methods

Unless otherwise noted, all calculations were performed at the DFT Becke3LYP level of theory.[9−11] Autogenerated delocalized coordinates[12] were used for geometry optimizations, using a medium-sized basis set, 6-31+G(d,p). More accurate energies of the optimized geometries were calculated with a triple-ζ quality basis set, 6-311+G(3d,2p). In reactions including Fe or Br species, the SBKJC effective-core potential[13] was used for Fe or Br. Zero-point (ZPE) and thermal effects ($T = 298.15$ K, $P = 1$ bar) were evaluated by using a scaling factor of 0.9857 for the computed frequencies.[14] Redox potentials were computed at the ROMP2 level with the 6-311+G(3d,2p) basis set as the energy differences between the geometry-optimized neutral and cationic species. Reorganization energies (computed at the B3LYP/6-311+G(3d,2p) level) of the redox reactions were obtained by using the neutral structure for the cationic state, and the cationic structure for the neutral state. Solvation effects (in dichloromethane) were computed by applying the polarizable conductor model (CPCM),[15−17] as implemented in PcGamess,[18] on gas phase optimized geometries. All solution energies presented include electrostatic and cavitation energies. Computation of dispersion and repulsion effects was performed as described by Amovilli and Mennucci.[19] Computation of these effects is only implemented for systems with null spin, and therefore could only by performed on the reactions with methyleneiminium cations and with NO_2^+. Except for CPCM calculations in steps involving paramagnetic species, which do not include dispersion or repulsion effects and were performed with Gamess-US[20] (22nd February 2006 release), all calculations were performed with the PcGamess software package. Computation of natural atomic charges[21] and natural resonance theory analysis[22−24] were performed with NBO 5.G.[25] Electrostatic potentials of selected compounds were computed from NBO charges and mapped on the molecules' van der Waals surfaces.

III. Results and Discussion

To perform a study of a representative number of 1,2-azaborine derivatives, we performed computations with a large number of ring substituents, which were chosen based on their presence on actual synthesized 1,2-azaborines. Computations with the corresponding benzene derivatives then afford both a convenient comparison scale and the possibility of validation of the computational methods employed. The most salient points of our results are gathered in Table 1.

One-Electron Oxidation of Substituted 1,2-Azaborines. One-electron oxidation of substituted 1,2-azaborines generally results in similar geometric changes: a 0.03−0.06 Å increase in the N_1-B_2 and C_5-C_6 bond lengths, and a 0.03−0.05 Å shortening of the C_6-N_1 bond. The most notable exception to this general trend arises with 2-formyl-1,2-azaborine, whose geometry changes very little upon oxidation: its reorganization energy (Table 1) is accordingly the lowest among all studied derivatives. Inspection of the electrostatic potentials on the cationic forms of these species (Figures 1 and 2) reveals that oxidized N-substituted azaborines generally present more variation in electrostatic potential across the ring than corresponding boron-substituted azaborines, and that the most intense locus of positive

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TABLE 1. An Overview of the Reactivity of Substituted 1,2-Azaborines

reaction	N-substituted azaborines	B-substituted azaborines	most dramatic substituent effects (vs. benzene analogues)
oxidation	no clear trend vs. benzene analogues	better reductants than benzene analogues	formyl (on B): better reductant by 2.1 V formyl (on N): better reductant by 0.9 V amino (on N): worse reductant by 0.3 V
nitration	generally more favorable than in benzene analogues, except with OH−, NH_2− or SH− substituents; yields preferentially 1,2-azaborinyl nitrites rather than C_3-nitrated products	more favorable than in benzene analogues; yields C_3-nitrated products	formyl-substituted azaborines are not deactivated, in contrast to the effect of formyl on benzene; N-substituted azaborines: chlorine and thiol slightly deactivating; in contrast to its effect on benzene, hydroxyl deactivates 1,2-azaborine and NH_2 barely activate it
halogenation	more favorable than in benzene analogues; yields preferentially boron-halogenated rather than C_3-halogenated products	more favorable than in benzene analogues; yields C_3-nitrated products	NH_2 has a deactivating effect when bound to the nitrogen atom on 1,2-azaborine, but an activating effect when bound to the boron atom
acylation	generally more favorable than in benzene analogues; yields C_3-acylated products; with NH_2- substituent the C_5 product lies < 3 kcal·mol^{-1} higher than C_3-products	more favorable than in benzene analogues; yields C_3-acylated products; with SH− substituent the C_5 product lies < 3 kcal·mol^{-1} higher than C_3-products	when bound to benzene or to the azaborine through the boron atom, NH_2− is the most activating substituent; when bound to the azaborine through the nitrogen atom, phenyl is the most activating substituent
Mannich reaction	generally more favorable than in benzene analogues; C_5-product usually lies < 4 kcal·mol^{-1} higher than C_3-products	more favorable than in benzene analogues; C_5-product usually lies < 4 kcal·mol^{-1} higher than C_3-products	1-amino-1,2-azaborine is less active than its benzene analogue; SH− and OH− have deactivating effects on 1,2-azaborine when bound to its nitrogen atom (but not when bound to its boron atom)

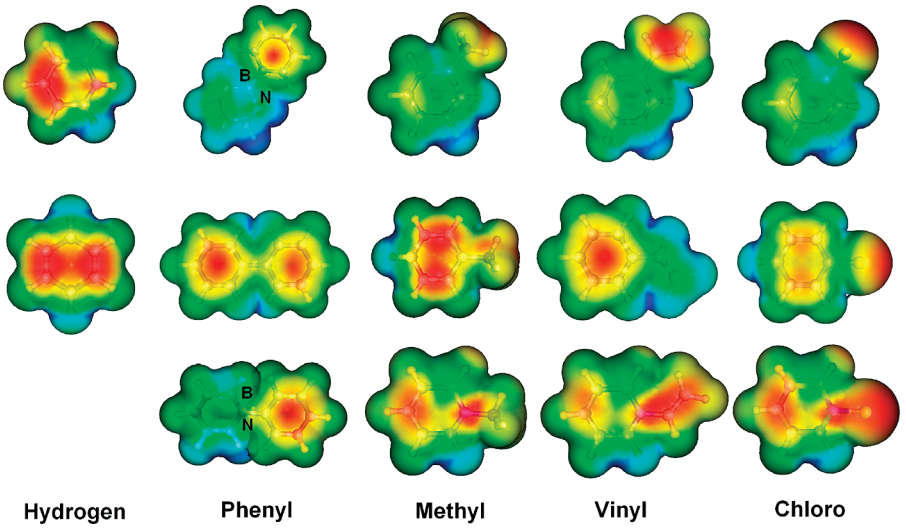

FIGURE 1. Electrostatic potentials of the cationic forms of selected benzene/azaborine derivatives. In each compound, the most positive electrostatic potential regions are depicted in blue; red shows the areas with smaller positive charge. The precise electrostatic potential ranges for each molecule can be consulted in Table S28 (Supporting Information). Column labels show the substituent appended to the aromatic system: (first row) B-substituted 1,2-azaborine derivatives; (central row) benzene derivatives; (bottom row) N-substituted 1,2-azaborine derivatives. For ease of comparison 1,2-azaborine derivatives are always depicted with nitrogen on the right side of the ring, and boron at the 1 o'clock position. These positions are explicitly highlighted in the phenylated derivatives.

charge on oxidized azaborines tends to occur on the C_6 position. Observation of the electrostatic potentials of the cationic phenyl-substituted azaborines shows that the lost electron comes mostly from the azaborine moiety (rather than the phenyl system), i.e., azaborine is a better reductant than benzene.

Since the reduction potentials of one-electron oxidized benzene derivatives we computed at the B3LYP/6-311+G-(3d,2p) level combination differed approximately 0.3 V from the experimental[26] values, we performed higher-level computations at the restricted open-shell MP2 level, using the B3LYP/6-31+G(d,p) optimized geometries. The reduction potential values computed at this level show excellent agreement with the experimental ionization potential values (Table 2), and we expect the computed reduction potentials for the substituted 1,2-azaborines to be of comparable quality. The predicted reduction potential of the parent compound, 1,2-dihydro-1,2-azaborine$^{\bullet+}$, was found to be ≈0.7 V lower than that of benzene$^{\bullet+}$. In all cases, B-substituted 1,2-azaborines prove to be better reductants than the

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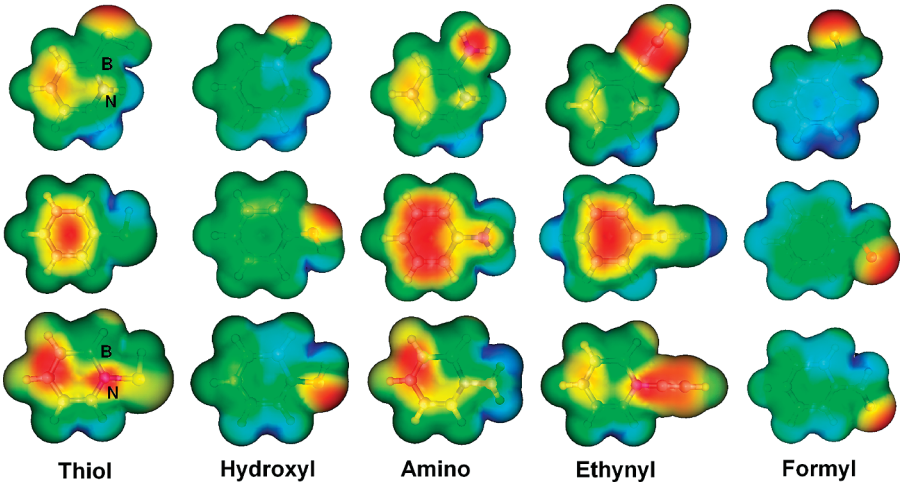

FIGURE 2. Electrostatic potentials of the cationic forms of selected benzene/azaborine derivatives. In each compound, the most positive electrostatic potential regions are depicted in blue; red shows the areas with smaller positive charge. The precise electrostatic potential ranges for each molecule can be consulted in Table S28 (Supporting Information). Column labels show the substituent appended to the aromatic system: (first row) B-substituted 1,2-azaborine derivatives; (central row) benzene derivatives; (bottom row) N-substituted 1,2-azaborine derivatives. For ease of comparison 1,2-azaborine derivatives are always depicted with nitrogen on the right side of the ring, and boron at the 1 o'clock position. These positions are explicitly highlighted in the thiolated derivatives.

TABLE 2. Computed Absolute Reduction Potentials (in the Gas Phase) and Reorganization Energies of the Cationic Forms of Substituted 1,2-Azaborines (at 0 K)[a]

	absolute reduction potential (V)				reoganization energy (kcal·mol^{-1})		
substituent	benzene deriv(ref values)	benzene deriva(computed)	N-substituted 1,2-azaborines (computed)	B-substituted 1,2-azaborines (computed)	benzene deriv	N-substituted 1,2-azaborines	B-substituted 1,2-azaborines
hydrogen	9.24	9.26	8.50	8.50	6.62	7.73	7.73
phenyl	8.16	8.11	8.20	7.92	8.46	6.26	5.92
methyl	8.83	8.85	8.27	8.21	7.51	8.05	8.90
vinyl	8.46	8.49	8.27	8.09	6.49	5.72	6.57
chloro	9.07	9.05	8.68	8.50	7.70	7.88	9.19
thiol	8.30	8.22	8.52	8.11	5.38	12.54	5.98
hydroxyl	8.49	8.50	8.49	8.01	8.93	7.65	9.93
amino	7.72	7.68	8.00	7.55	10.74	21.89	6.70
ethynyl	8.82	8.77	8.61	8.32	5.53	5.74	6.72
formyl	9.50	9.63	8.70	7.55	7.97	9.78	2.35

[a]Thermal effects at 298 K amount to <2 kcal·mol^{-1} (i.e., <0.1 V) in every case, and are omitted for ease of comparison with the experimental ionization potential values.

TABLE 3. Computed Absolute Reduction Potentials in Dichloromethane and Reorganization Energies of the Cationic Forms of Substituted 1, 2-Azaborines[a]

	absolute reduction potential (V)			reoganization energy (kcal·mol^{-1})		
substituent	benzene deriv (computed)	N-substituted 1,2-azaborines (computed)	B-substituted 1,2-azaborines (computed)	benzene derivatives	N-substituted 1,2-azaborines	B-substituted 1,2-azaborines
hydrogen	7.25	6.52	6.52	6.37	7.29	7.29
phenyl	6.51	6.59	6.31	8.37	6.02	6.02
methyl	6.95	6.40	6.31	7.33	7.49	8.39
vinyl	6.70	6.47	6.29	6.41	5.53	6.46
chloro	7.15	6.75	6.56	7.65	7.55	8.75
thiol	6.36	6.65	6.27	5.39	11.07	6.12
hydroxyl	6.57	6.56	6.12	8.63	7.28	9.10
amino	5.78	6.10	5.71	10.47	21.40	6.43
ethynyl	7.00	6.79	6.53	5.42	5.78	6.59
formyl	7.73	6.79	5.73	7.42	8.43	1.25

[a]Solvation effects were computed at the B3LYP/6-311+G(3d,2p) level. The absolute reduction potential of the standard hydrogen electrode, in water, is 4.43 V.[27].

corresponding benzene derivatives. The smallest differences (≈0.1 V) arise in the comparison between 2-amino-1,2-azaborine and 2-mercapto-1,2-azaborine with their aniline and benzenethiol counterparts. Substitution on the nitrogen atom of 1,2-azaborines affords a much more erratic behavior: some derivatives are better reductants than their benzene counterparts, whereas, e.g., 1-amino-1,2-azaborine is more difficult to oxidize than its analogue, aniline. N-Substituted

TABLE 4. Computed Free Energies (in Dichloromethane Solution) of the Nitration ($NO_2^+ + R \rightarrow RNO_2^+$) and Chlorination Reactions ($FeCl_3 + Cl_2 + R \rightarrow FeCl_4^- + RCl^+$) of Benzene Derivatives[a]

	nitration			chlorination		
substituent	ortho	meta	para	ortho	meta	para
hydrogen	2.0	2.0	2.0	−12.9	−12.9	−12.9
phenyl	−9.1	−3.4	−13.8	−18.5	−11.8	−21.6
methyl	−7.4	−6.3	−11.2	−18.0	−14.6	−20.2
vinyl	−8.4	−3.6	−14.0	−18.3	−11.7	−21.3
chloro	1.6	3.1	−4.0	−9.7	−5.8	−12.5
thiol	−9.6	−0.9	−15.7	−19.9	−9.1	−24.4
hydroxyl	−15.4	−2.8	−19.6	−22.9	−11.2	−27.6
amino	−29.0	−8.1	−35.7	−37.4	−15.7	−43.0
ethynyl	−2.1	1.2	−5.0	−12.3	−7.3	−14.0
formyl	10.5	3.8	10.1	−2.4	−5.0	−2.8
N-bound 1,2-azaborine	−4.8	0.6	−10.9	−17.2	−9.0	−20.8
B-bound 1,2-azaborine	−11.6	−6.9	−15.1	−20.8	−16.2	−23.0

[a]All data in kcal·mol^{-1}. ZPE and thermal effects computed at 298.15 K.

1,2-azaborines are generally worse reductants than the corresponding B-substituted compounds. Computed reduction potentials in dichloromethane closely follow the gas phase trends (Table 3).

According to Marcus theory, the activation energies of outer-sphere electron transfer reactions depend not only on the reduction potentials but also on the reorganization energy of the system. For each of the studied species (and their one-electron oxidized counterparts) we evaluated the corresponding reorganization energies by computing the electronic energies of the oxidized structure for the reduced state, and the reduced structure for the oxidized state. In almost all cases, differences in reorganization energies of the electron self-exchange reactions ($A + A^+ \rightarrow A^+ + A$) amounted to less than 8 kcal·mol^{-1} (Table 2). The most notable exception is (again) 1-amino-1,2-azaborine, which is less reactive than its arene counterpart, aniline, in self-exchange electron transfer reactions. This observation raises the possibility of using 1-amino-1,2-azaborines as a (somewhat less reactive) substitute of anilines.

1,2-Azaborine as a Benzene Substituent. The energies of nitration and chlorination intermediates of selected benzene derivatives were computed as described in the Methods section, and compared with N- and B-bound 1,2-azaborine. The results clearly show that 1,2-azaborine is a benzene-activating substituent, which stabilizes the para and ortho intermediates of their electrophilic aromatic substitution reactions (Table 4). The effect of 1,2-azaborines is similar to that of vinyl and thiol substitutents (slightly smaller than that of OH) and seems to be slightly larger when it is bound to the benzene ring through its boron atom. However, since the 1,2-azaborine ring is much more reactive than benzene in electrophilic aromatic substitutions (see full results below), its potential use as a benzene-activating group is expected to be quite limited.

TABLE 5. Computed Free Energies (in Dichloromethane Solution) of the Nitration Reactions ($NO_2^+ + R \rightarrow RNO_2^+$) of 1,2-Azaborine Derivatives[a]

substituents	1a	1b	1c	1d	1e	2
hydrogen	−25.8			−13.9		−27.2
phenyl (on N)	−24.5	5.4	n.d.	−16.6		−27.6
methyl (on N)	−27.7	→ **1c**	−30.9	−20.8		−30.5
vinyl (on N)	−25.8	5.1	n.d.	−17.7		−27.4
chloro (on N)	→ **2**			−9.5		−22.7
thiol (on N)	→ **2**	6.2	n.d.	−15.3		−26.6
hydroxyl (on N)	−21.3	8.1	n.d.	−14.8		−27.2
amino (on N)	→ **2**	→ **1c**	−33.3	−22.3	−5.3	−33.4
ethynyl (on N)	−17.9			−7.2		−22.9
formyl (on N)	−15.0			−5.7		−21.0
phenyl (on B)	−29.8			−23.4		−25.7
methyl (on B)	−28.8	→ **1c**	−34.3	−22.9		−28.7
vinyl (on B)	−29.3			−22.1		−25.9
chloro (on B)	−20.5			−15.7		−21.3
thiol (on B)	−29.3	→ **1c**	−32.2	−23.2		−22.3
hydroxyl (on B)	−33.5			−27.2		−28.0
amino (on B)	−43.2	→ **1c**	−44.4	−34.5		→ **1a**
ethynyl (on B)	−23.5			−17.5		−22.9
formyl (on B)	→ **2**			−8.9		−22.4

[a]All data in kcal·mol^{-1}. ZPE and thermal effects computed at 298.15 K. Instances where an intermediate spontaneously collapses into a different structure are highlighted. Blank fields mean that the structures could not be found as minima on the potential energy surface after geometry optimization. n.d.: not optimized.

Nitration. Nitration of benzene derivatives has been extensively studied by theoretical methods:[28−31] upon formation of a loosely bound π-complex between NO_2^+ and the aromatic ring (ArX), either a single-electron transfer from the ring to the NO_2^+ moiety or direct electrophilic attack (depending on the ring substituents, reactants ionization potentials, etc.) leads to the formation of the well-known "arenium ion" intermediate ($ArXNO_2^+$), also known as the σ-complex or the "Wheland intermediate", **1a**, **1b**, **1d**, and **1e**. The presence of substituents on the aromatic ring affects the regioselectivity of the reaction by differentially stabilizing the ortho, meta, and para positions of the aromatic ring. The transition states leading to the Wheland intermediates lie very low in energy, so that regioselectivity is mostly determined by the relative thermodynamic stabilities of the Wheland intermediates.[28,29]

We computed the energies of every Wheland intermediate arising from nitration of selected N- or B-substituted azaborines (Table 5). A Wheland intermediate (with a very high energy) on C_6 (**1e**) could only be found on 1-amino-1,2-azaborine. Nitration at the C_4-position (**1b**) afforded the least stable intermediates, which is consistent with the limited resonance landscape available at that position. In several cases, the intermediate on C_4 is so high in energy that a hydride spontaneously moves from C_4 to C_3 in order to yield a much more stable configuration with larger resonance possibilities (**1c**). Electrophilic attack on C_5 (**1d**) yielded intermediates 5−14 kcal·mol^{-1} higher in energy than on the remaining C_3 position (**1a**), which is clearly favored in every instance, even in the presence of electron-withdrawing substituents. Nitration on C_3 may afford either the regular Wheland intermediate (**1a**) or a novel bicyclic intermediate (**2**, Scheme 2) where an oxygen atom from the NO_2^+ electrophile engages the electron-deficient boron atom. In B-substituted 1,2-azaborines,

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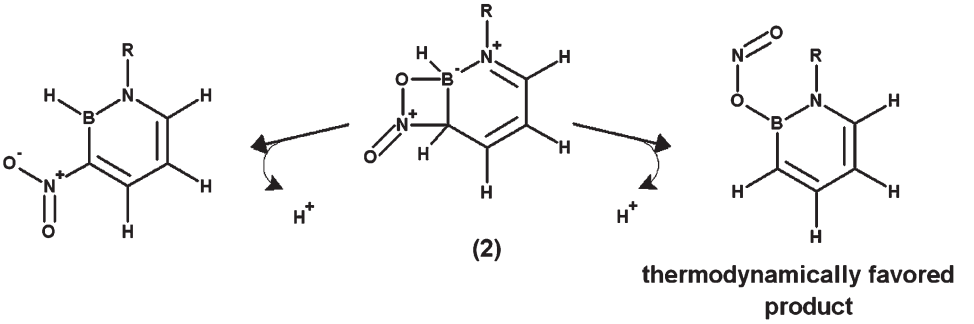
SCHEME 2. Possible Fates of the Bicyclic Interemediates Arising from Nitration of N-Substituted 1,2-Dihydro-1,2-azaborines



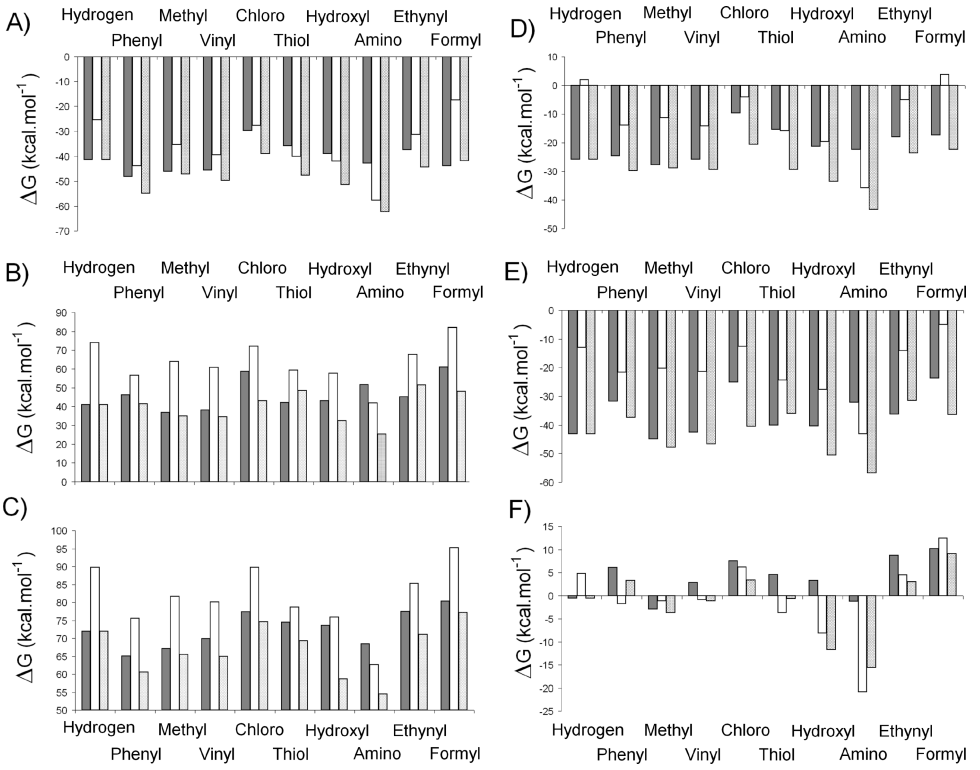


FIGURE 3. Gas phase (A−C) and solution (D−F) free energies (relative to isolated reactants) of the most stable Wheland intermediates in nitration (A/D), chlorination (B/E), and acylation (C/F) of substituted benzenes (white bars), N-substituted 1,2-azaborines (gray bars), and B-substituted 1,2-azaborines (dotted bars). The most stable Wheland intermediate is usually (**1a**), except in nitration reactions of N-substituted 1,2-azaborines, where the Wheland intermediate (**1a**) is not stable due to collapsing into the novel intermediate (**2**), and in the chlorination of N-amino-substituted 1,2-azaborine.

this intermediate lies at slightly higher energies than the regular σ-complex (**1a**). However, in 1,2-azaborines bearing a hydrogen on the boron atom it lies a few kilocalories per mole below **1a**. In these cases, loss of the boron-bound H^+ leads to an electronic rearrangement that breaks the incipient C_3-NO_2 bond and yields novel 1,2-azaborinyl nitrites. The compounds thus obtained are 26−28 kcal·mol^{-1} more stable (see the Supporting Information) than the corresponding C_3-nitrated analogues obtained through loss of H^+ from **1a**, and further increase the range of molecular scaffolds available from these interesting aromatic compounds.

In the corresponding benzene derivatives, nitration is known to be consistently favored on the ortho and para positions (except in the deactivated benzaldehyde ring). Comparison of the energies of the postulated Wheland intermediates with the isolated reactants shows that the bare 1,2-azaborine is a highly activated ring, since nitration of 1,2-azaborine is much more favorable than that of any of the tested benzene derivatives except phenol, aniline, and phenylbenzene (Figure 3A). The effect of substitutions on the reactivity of the 1,2-azaborines is generally less dramatic than that on benzene, especially if the substitution occurs on the nitrogen atom. Boron-substituted 1,2-azaborines are generally more reactive than the corresponding nitrogen-substituted 1,2-azaborines. As expected from the charged nature of the electrophile, solvation stabilizes reactants more effectively than the Wheland intermediates (where the positive charge is delocalized through the conjugated system), so that the reactions become ≈15−30 kcal·mol^{-1} less favorable.

TABLE 6. Computed Free Energies (in Dichloromethane Solution) of the Chlorination Reactions ($FeCl_3 + Cl_2 + R \rightarrow FeCl_4^- + RCl^+$) of 1,2-Azaborine Derivatives[a]

substituents	1a	1b	1c	1d	1e
hydrogen	−31.4		−43.1	−26.8	
phenyl (on N)	−31.6			−26.8	
methyl (on N)	−34.2		−44.9	−30.3	−12.7
vinyl (on N)	−32.0		−42.6	−27.2	−10.9
chloro (on N)	−25.1			−17.4	
thiol (on N)	−29.7		−40.0	−24.5	−8.9
hydroxyl (on N)	−29.8		−40.4	−25.9	−8.9
amino (on N)	(−41.4)[b]	−11.3	n.d.	−32.0	−15.1
ethynyl (on N)	−25.0		−36.2	−18.7	−7.6
formyl (on N)	−23.7			−16.8	
phenyl (on B)	−37.2			−33.5	
methyl (on B)	−37.4		−47.8	−32.5	
vinyl (on B)	−37.2		−46.6	−32.3	
chloro (on B)	−29.5		−40.4	−25.4	
thiol (on B)	−35.9			−32.0	
hydroxyl (on B)	−40.9		−50.5	−36.1	
amino (on B)	−48.7		−56.7	−44.0	
ethynyl (on B)	−31.4			−27.1	
formyl (on B)	−24.0		−36.3	−19.6	−5.5

[a]All data in kcal·mol^{-1}. ZPE and thermal effects computed at 298.15 K. Blank fields mean that the structures could not be found as minima on the potential energy surface after geometry optimization. [b]Intermediate bound on boron, rather than on C3.

Surprisingly, OH− was found to have a **deactivating** effect on 1,2-azaborine when bound to its nitrogen atom, in contrast to its strong activating effect on benzene. To gain further insight into this unexpected observation, we analyzed the electron distributions on the 1,2-azaborine (and benzene) derivatives using Natural Bond Orbital[21] and Natural Resonance theories.[22−24] Analysis of the natural electron populations on the ring atoms (see the Supporting Information, Tables S26 and S27) shows that in all studied 1,2-azaborines C_3 carries the largest negative charge (−0.46 to −0.54) of all carbon atoms, followed by C_5 (−0.27 to −0.32), in agreement with the significant reactivity at these positions. Substituent effects on the partial charges of N-substituted 1,2-azaborines at the (most reactive) C_3 position are negligible (< 0.01 e$^-$), and are also very small at the C_5 atom (0.01−0.02 e$^-$), the other reactive position. The effects on the partial charges at the C_3 position of boron-substituted 1,2-azaborines are larger (0.01−0.035 e$^-$), but still lower than those observed at the ortho or para positions of benzene derivatives (0.01−0.08 e$^-$). These trends agree reasonably well with the observation of smaller substituent effects on the reactivity of N-substituted than on B-substituted 1,2-azaborines. Inspection of the contributing resonance forms yielded more interesting details on the origin of the different behaviors of substituted 1,2-azaborines: the substitution of the nitrogen-bound H atom by OH yields an electronic distribution in which the second-most important resonance structure (11.5% contribution) has an ***electrophilic*** C_3 atom, instead of the ***nucleophilic*** resonance structures most frequently observed with the other azaborines, which explains the unexpected low reactivity of this azaborine. Important electrophilic resonance structures are also observed on 1,2-azaborines N-substituted with NH_2 (8.8% contribution) or ethynyl (9.8%), which are indeed less reactive (vs. 1,2-azaborine) than expected from their influence on benzene.

Halogenation. Chlorination of most benzene derivatives requires the use of Lewis acids (such as $FeCl_3$ or $AlCl_3$) to facilitate the heterolytical cleavage of Cl_2 into Cl^- and the reactive Cl^+ electrophile. Although we found the addition of Cl^+ to benzene derivatives or 1,2-azaborines to be highly exergonic (−110 to −170 kcal·mol^{-1} in the gas phase, and −120 to −150 kcal·mol^{-1} in solution), the formation of Cl^+ from Cl_2 and $FeCl_3$ is not at all spontaneous, since it is endergonic by approximately 200 kcal·mol^{-1} in the gas phase (and 90 kcal·mol^{-1} in solution since the electrostatic stabilization of the (charged) products is much more important than that of the neutral reactants). The reaction must therefore proceed through the formation of a ternary complex R-Cl-Cl-$FeCl_3$, as already suggested by lower level computations on the halogenation of benzene[32] and for Friedel−Crafts alkylations.[33] In agreement with the neutral character of the reactants and the charged nature of the intermediate, our computations show that solvation makes the chlorination reactions of benzene and 1,2-azaborine derivatives ≈75−85 kcal·mol^{-1} more favorable than in the gas phase.

As expected from the natural population analysis described in Tables S26 and S27 of the Supporting Information, attack on C_3 yields the most stable Wheland intermediates, followed by attack on C_5. Except for the N-amino-substituted 1,2-azaborine, the energy differences between these intermediates are relatively small (3.8−7.6 kcal·mol^{-1}) (Table 6), and therefore the reaction may afford a mixture

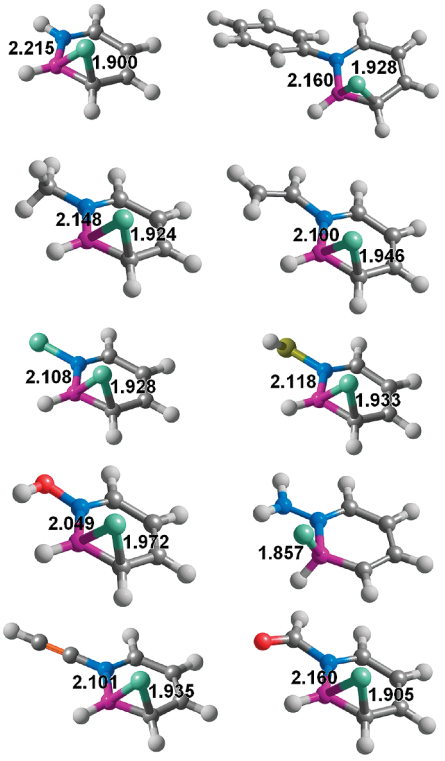


FIGURE 4. Gas phase geometries of the intermediates arising from Cl^+ addition to the C_3 atom in N-substituted 1,2-azaborines. B−Cl and C_3−Cl distances (in Å) are shown. Substitutents bound to the nitrogen atom are (from left to right, and from top to bottom) the following: H, phenyl, methyl, vinyl, Cl, SH,OH, NH_2, ethynyl, and formyl.

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TABLE 7. Computed Free Energies of the Bromination Reactions ($Br_2 + R \rightarrow Br^- + RBr^+$) of Phenylated 1,2-Azaborine Derivatives[a]

	gas phase		solution	
substituents	**1a**	**1d**	**1a**	**1d**
phenyl (on N)	104.0	110.7	6.3	13.3
Phenyl (on B)	102.2	106.7	3.9	8.3

[a]All data in kcal·mol^{-1}. ZPE and thermal effects computed at 298.15 K.

TABLE 8. Computed Free Energies (in Dichloromethane Solution) of the Acylation Reactions ($FeCl_3 + HCOCl + R \rightarrow FeCl_4^- + HCOR^+$) of 1,2-Azaborine Derivatives[a]

substituents	**1a**	**1b**	**1d**	**1e**	cyclic **1a**
hydrogen	−0.6		4.4	18.5	4.3
phenyl (on N)	6.1	35.2	12.6	26.4	13.1
methyl (on N)	−3.0		2.3	→ **1d**	3.5
vinyl (on N)	2.9		7.0	20.8	7.5
chloro (on N)	7.5		13.6	22.6	9.7
thiol (on N)	4.6		8.5	20.4	7.2
hydroxyl (on N)	3.3		6.9	20.1	5.7
amino (on N)	−1.3		1.3	15.6	0.8
ethynyl (on N)	8.7		13.6	22.6	10.8
formyl (on N)	10.2		16.4	24.9	12.0
phenyl (on B)	3.3		7.0	→ **1d**	14.6
methyl (on B)	−3.7		1.1	→ **1d**	4.5
vinyl (on B)	−1.2		2.1	→ **1d**	8.2
chloro (on B)	3.4		7.6	22.0	10.4
thiol (on B)	−0.7		2.0	18.9	9.3
hydroxyl (on B)	−11.7		−2.8	15.9	→ **1a**
amino (on B)	−15.6		−9.3	12.8	→ **1a**
ethynyl (on B)	3.0		6.5	22.3	10.6
formyl (on B)	9.1		12.4	26.1	11.1

[a]All data in kcal·mol^{-1}. ZPE and thermal effects computed at 298.15 K. Instances where an intermediate spontaneously collapses into a different structure are highlighted. Blank fields mean that the structures could not be found as minima on the potential energy surface after geometry optimization.

of C_3- and C_5-substituted products under some experimental conditions. Interestingly, in the intermediates arising from attack on C_3 of N-substituted 1,2 azaborines Cl^+ migrates to a "bridging" position above the C_3−B bond (Figure 4), and in the amino-substituted derivative, Cl^+ added to C_3 fully migrates to the boron atom. Loss of H^+ from these intermediates is ≈30 kcal·mol^{-1} more favorable from boron than from C_3, and these reactions are therefore predicted to yield boron-chlorinated azaborines, rather than carbon-chlorinated compounds. Our computations therefore show that chlorination of the *carbon* atoms of 1,2-azaborines is only feasible on boron-substituted 1,2-azaborines.

Although there are, at present, no experimental reports of chlorination taking place on 1,2-azaborines, bromination of substituted 1-ethyl-2-phenyl-1,2-azaborine has been shown[6] to yield products substituted on C_3. Computations on 2-phenyl-1,2-azaborine predict that substitution is expected to occur preferentially on the C_3 position (Table 7), in agreement with the experimental observations. As predicted above for chlorination reactions, bromination of the N-substituted 1-phenyl-1,2-azaborine yields an intermediate with the halogen on a bridging position between the boron atom and C_3, which preferentially collapses into a boron-brominated (rather than C_3-brominated) product. The B-bound product is preferred over the C_3-bound molecule by 26.9 kcal·mol^{-1}, a value similar to that observed in the related chlorination reactions.

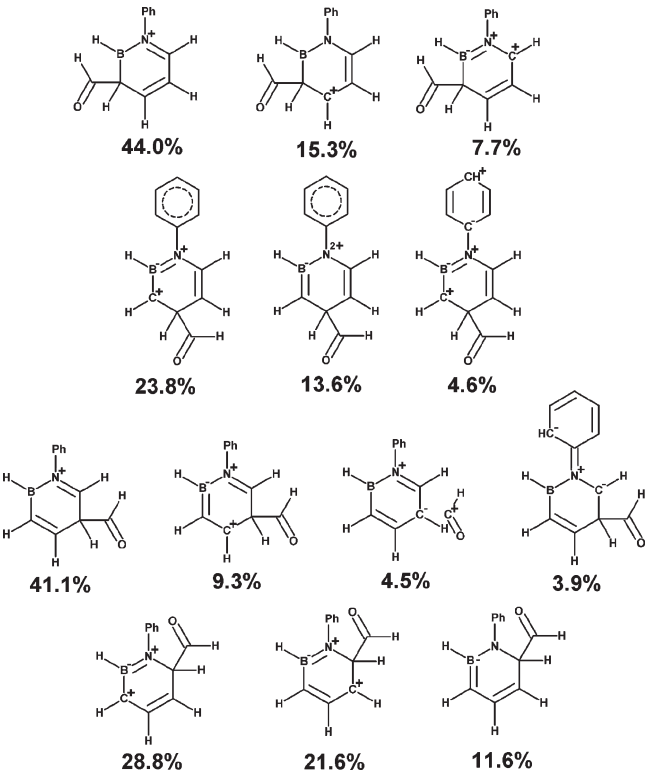

FIGURE 5. Most important contributing resonance structures for the σ-complexes formed from addition of formyl cation to 1-phenyl-1,2-azaborine, as computed by Natural Resonance Theory.

Acylation. The reaction mechanism of metal chlorides-assisted Friedel−Crafts acylation of aromatic compounds is known to be quite complex: Lewis acid complexation to either the carbonyl[34,35] or the halogen[36,37] of the acyl chloride has been described, as well as additional complexation of a second Lewis acid molecule to an acylium cation intermediate,[38] and more complex kinetical models[39] including fourth-order rate constants and inhibition of the Lewis acid by product. Our computations show that, like chlorination, Friedel−Crafts acylation (using $FeCl_3$ as Lewis acid) must proceed in the gas phase through the formation of some kind of ternary complex (e.g., R-HC═O-Cl-$FeCl_3$), since the formation of HCO^+ from HCOCl and $FeCl_3$ is too unfavorable ($\Delta G = 119.5$ kcal·mol^{-1}in gas phase). In solution, such a ternary complex does not appear to be required on thermodynamic grounds, since solvation effects make HCO^+ formation feasible ($\Delta G = 6.4$ kcal·mol^{-1}).

The gas phase stability of the Wheland intermediates formed upon acylation of substituted 1,2-azaborines (Supporting Information, Table S7) broadly follows the trends reported above for nitration and chlorination reactions: C_3-bound intermediates are favored (by

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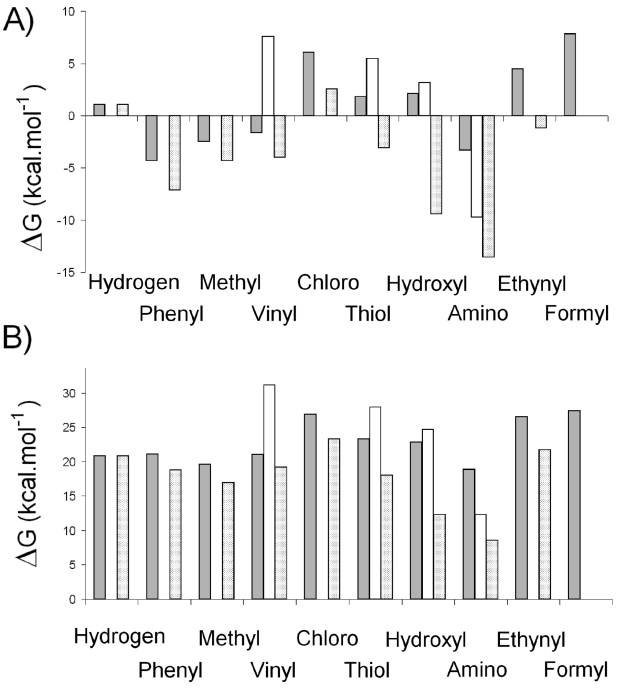

FIGURE 6. Gas phase (A) and solution (B) free energies (relative to isolated reactants) of the most stable Wheland intermediates in methyleneiminium cation addition to substituted benzenes (white bars), N-substituted 1,2-azaborines (gray bars) and B-substituted 1,2-azaborines (dotted bars). No stable intermediates could be found in the reactions with benzene, phenylbenzene, toluene, chlorobenzene, ethnylbenzene, benzaldehyde, or 2-formyl-1,2-azaborine.

2.5−8.9 kcal·mol^{-1}) over C_5-bound intermediates for all studied molecules; C_4-bound and C_6-bound intermediates are strongly disfavored. The effects of solvation (Table 8) are, however, less uniform than those observed for the other studied reactions: in particular, no N-substituted 1,2-azaborine is substantially more reactive than the bare 1,2-azaborine, and only very strong substituents (OH, NH_2) on boron have noticeable activating effects.

Interestingly, stable Wheland intermediates on ***every*** carbon atom of a substituted 1,2-azaborine ring could be found in the acylation reactions of 1-phenyl-1,2-azaborine. These intermediates afford a convenient set of structures for the study of the relative importance of the different resonance structures stabilizing the different σ-complexes (Figure 5). Analysis of the electron densities in these intermediates with Natural Resonance Theory shows that in the most unstable intermediates (C_2- and C_4-bound) the most-heavily weighted resonance structures contain several point charges that cannot be efficiently delocalized throughout the ring, whereas in the most stable σ-complexes the most heavily weighted resonance structures have a positive charge on the ring nitrogen atom.

Mannich Reactions with Methyleneiminium Cations. In their experimental study of electrophilic aromatic substitution in 1,2-azaborines, Pan et al.[6] described a consistent trend for substitution to occur at the C_3 position. The reactions with methyleneiminium cations, however, yielded C_5-substituted products. Our computations on these reactions show that the methyleneiminium cation is a very poor electrophile: in reactions with benzene derivatives, Wheland intermediates could only be found in the presence of strong activating substituents (Figure 6). Reactions with substituted 1,2-azaborines were more favorable and followed the trends observed in the other electrophilic substitutions studied above, with boron-substituted 1,2-azaborines generally more reactive than the corresponding nitrogen-substituted molecules (with the notable exception of B-formylated 1,2-azaborines, which do not react at all). The energy differences between the C_3 and C_5 Wheland intermediates in these reactions (Table 9) were found to be the smallest among the electrophilic substitution reactions we studied (often only a couple of kilocalories per mole) and these reactions are therefore expected to yield larger amounts of C_5-substituted products than either nitration, chlorination, or acylation. Comparison with experimental results by Pan et al.[6] affords a test of our computational methods: the computations show that the C_3 and C_5 intermediates of the reaction of *N*,*N*′-dimethylmethyleneiminium cation with 1-ethyl-1,2-dihydro-2-phenyl-1,2-azaborine (which has been shown[6] to yield the C_5-substituted product) differ in energy by less than 0.2 kcal·mol^{-1} (1.5 kcal·mol^{-1} in gas phase), and that deprotonation of the C_5 Wheland intermediates affords a more stable product (by 7.4 kcal·mol^{-1}) than the one formed upon electrophilic substitution on C_3.

TABLE 9. Computed Free Energies (in Gas Phase and in Dichloromethane Solution) of the Reactions of 1,2-Azaborine Derivatives with Methyleneiminium Cations[a]

	gas phase		solution	
substituents	**1a**	**1d**	**1a**	**1d**
hydrogen	1.1		20.8	
phenyl (on N)	−4.3	0.0	21.1	25.4
methyl (on N)	−2.5	0.7	19.6	22.1
vinyl (on N)	−1.6	2.0	21.0	24.3
chloro (on N)	6.1		26.9	
thiol (on N)	1.8	5.6	23.3	26.8
hydroxyl (on N)	2.1	4.4	22.8	25.2
amino (on N)	−3.3	−1.3	18.9	20.1
ethynyl (on N)	4.5		26.5	
formyl (on N)	7.8		27.4	
phenyl (on B)	−7.1	−5.0	18.8	19.3
methyl (on B)	−4.3	−1.2	16.9	19.1
vinyl (on B)	−4.0	−2.0	19.2	19.9
chloro (on B)	2.6	6.4	23.3	26.0
thiol (on B)	−3.1	−0.6	18.0	19.9
hydroxyl (on B)	−9.4	−6.6	12.3	14.4
amino (on B)	−13.5	−10.3	8.6	10.7
ethynyl (on B)	−1.2	2.8	21.7	24.5
formyl (on B)				

[a] All data in kcal·mol^{-1}. ZPE and thermal effects computed at 298.15 K. Blank fields mean that the structures could not be found as minima on the potential energy surface after geometry optimization.

IV. Conclusions

The computations described in this paper afford interesting insights into the reactivity of a large array of 1,2-azaborines, and expand our knowledge of the chemistry of this promising class of compounds. In particular, 1,2-azaborines are shown to be usually better nucleophiles than corresponding benzene derivatives; 1,2-azaborines with an intact B−H bond afford the possibility of cross-reaction of some electrophiles with both the B atom and C_3, allowing the

synthesis of, e.g., a novel class of 1,2-azaborinyl nitrite compounds, and are usually better reductants than their benzene analogues. Comparison between the relative stabilities of C_3-bound and C_5-bound Wheland intermediates ;of different electrophilic substitution reactions of 1,2-azaborines further suggests that the preference of the C_3 over C_5 substitution decreases with decreasing electrophilicity of the attacking group (from >5 kcal·mol^{-1} difference in nitration, to >3 kcal·mol^{-1} in chlorination and acylation, to ≈ 2 kcal·mol^{-1} in reactions with methyleneiminium cations). Whether this observation reflects a broader trend or only a fortuitous coincidence remains to be tested experimentally.

Acknowledgment. The authors thank Derek Lowe (Vertex Pharmaceuticals) for bringing the subject to their attention.

Supporting Information Available: Geometries (computed at the B3LYP/6-31+G(d,p) level) of all species described in this paper, as well as their gas phase, ZPE, and thermal effects and solution energies (computed at the B3LYP/6-311+G(3d,2p) level, in CH_2Cl_2) and the most important resonance structures contributing to the computed electron densities of substituted benzenes and 1,2-azaborines, as predicted by Natural Resonance Theory. This material is available free of charge via the Internet at http://pubs.acs.org.