Computational studies on the reactivity of substituted 1,2-dihydro-1,2-azaborines

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Abstract:

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.

KEYWORDS: 1,2-azaborines; electrophilic aromatic substitution; density-functional theory; reactivity; $FeCl_3$

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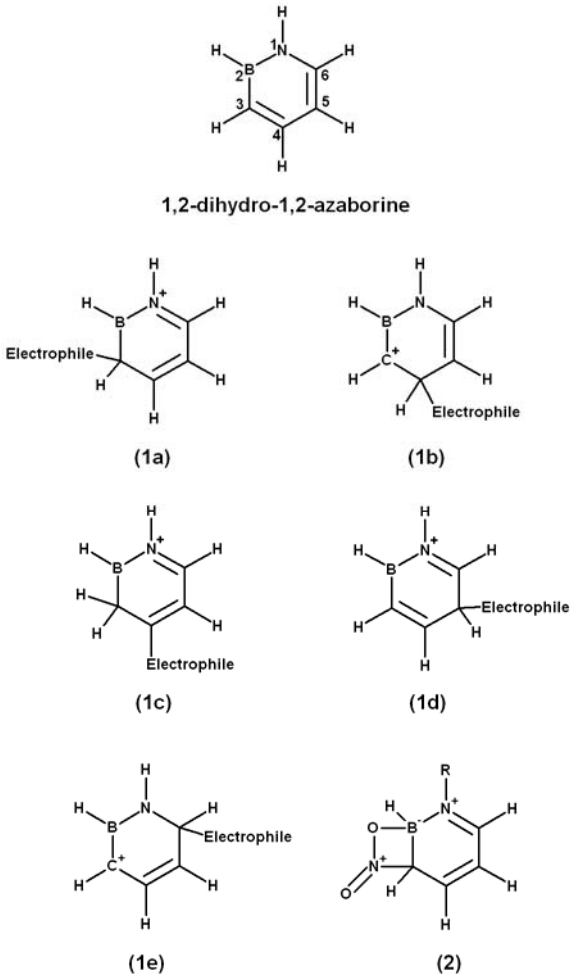
I. Introduction

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 1960's[1,2], but the chemistry of these compounds remained largely unexplored until the development (during the last decade) of new synthetic strategies[3,4,5,6] 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.



Sheme 1: 1,2-dihydro-1,2-azaborine and important intermediates in its electrophilic aromatic substitutions

In order 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.

II. Methods

All calculations were performed at the DFT Becke3LYP level of theory[9,10,11]. 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 species, the SBKJC effective-core potential[13] was used for Fe. Zero point (ZPE) and thermal effects (T=298.15 K, P=1 bar) were evaluated using a scaling factor of 0.9857 for the computed frequencies[14]. Redox potentials were computed as the energy differences between the geometry-optimized neutral and cationic species. Reorganization energies of the redox reactions were obtained 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[15,16,17], as implemented in PcGamess[18], on gas-phase optimized geometries. All solution energies presented include electrostatic and cavitation energies. Solution energies for the reactions with methyleniminium cations and with NO_2^+ also include dispersion and repulsion effects, which were evaluated as described by Amovilli and Mennucci[19]. Except for PCM calculations in steps involving paramagnetic species, which 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[22,23,24] were performed with NBO 5.G[25].

III. Results.

In order 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.

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.

The redox potentials of benzene derivatives computed with the basis set/theory level combination above agree reasonably well (Table 1) with the experimental values[26], and therefore we expect the computed redox potentials for the substituted 1,2-azaborines to be of comparable quality. The predicted redox potential of the parent compound, 1,2-dihydro-1,2-azaborine, was found to be ≈0.7 V lower than that of benzene. In all cases, B-substituted 1,2-azaborines prove to be better reductants than corresponding benzene derivatives. The smallest difference (0.14 V) arises in the comparison between 2-amino-1,2-azaborine and aniline. 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 counterpart, aniline. N-substituted 1,2-azaborines are generally worse reductants than the corresponding B-substituted compounds. Computed redox potentials in dicloromethane closely follow the gas phase trends (Table 2).

According to Marcus theory, the activation energies of outer-sphere electron transfer reactions depend not only on the redox 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 1). 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.

Table 1: Computed absolute redox potentials (in gas phase) and reorganization energies of substituted 1,2-azaborines.

	Absolute Redox potential (V)				Reoganization energy (kcal.mol^{-1})		
Substituent	**Benzene derivatives (reference values)**	**Benzene derivatives (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	9.24	8.94	8.21	8.21	6.62	7.73	7.73
Phenyl	8.16	7.76	7.77	7.42	8.46	6.26	5.92
Methyl	8.83	8.46	8.01	7.88	7.51	8.05	8.90
Vinyl	8.46	8.04	7.94	7.74	6.49	5.72	6.57
Chloro	9.07	8.71	8.41	8.20	7.70	7.88	9.19
Thiol	8.30	8.00	8.09	7.75	5.38	12.54	5.98
Hydroxyl	8.49	8.19	8.21	7.75	8.93	7.65	9.93
Amino	7.72	7.43	7.73	7.30	10.74	21.89	6.70
Ethynyl	8.82	8.37	8.27	7.96	5.53	5.74	6.72
Formyl	9.50	9.22	8.48	8.51	7.97	9.78	2.35

Table 2: Computed absolute redox potentials in dicloromethane and reorganization energies of substituted 1,2-azaborines. The absolute redox potential of the standard hydrogen electrode, in water, is 4.43 V[27].

	Absolute Redox potential (V)			Reoganization energy (kcal.mol^{-1})		
Substituent	**Benzene derivatives (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	6.94	6.23	6.23	6.37	7.29	7.29
Phenyl	6.16	6.16	5.81	8.37	6.02	6.02
Methyl	6.57	6.15	5.98	7.33	7.49	8.39
Vinyl	6.25	6.15	5.93	6.41	5.53	6.46
Chloro	6.81	6.48	6.26	7.65	7.55	8.75
Thiol	6.14	6.23	5.90	5.39	11.07	6.12
Hydroxyl	6.25	6.29	5.85	8.63	7.28	9.10
Amino	5.53	5.84	5.46	10.47	21.40	6.43
Ethynyl	6.60	6.46	6.17	5.42	5.78	6.59
Formyl	7.33	6.57	6.68	7.42	8.43	1.25

1,2-azaborine as a benzene substituent

The energies of nitration and chlorination intermediates of selected benzene derivatives were computed as described in Methods, 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 *orto*- intermediates of their electrophilic aromatic substitution reactions (Table 3). 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 3: Computed free energies (in dicloromethane 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 (in kcal.mol^{-1}). All data in kcal.mol^{-1}. ZPE and thermal effects computed at 298.15 K.

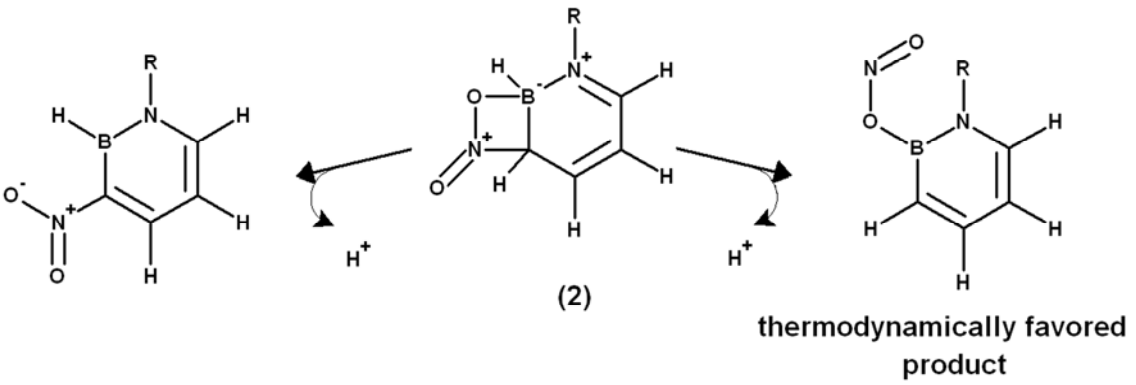
	Nitration			**Chlorination**		
Substituent	***orto-***	***meta-***	***para-***	***orto-***	***meta-***	***para-***
Hydrogen	2.0	2.0	2.0	-12.9	-12.9	-12.9
Phenyl	-9.1	-3.4	-13.8	-18.5	-11.8	-21.6
Methyl	-7.4	-6.3	-11.2	-18.0	-14.6	-20.2
Vinyl	-8.4	-3.6	-14.0	-18.3	-11.7	-21.3
Chloro	1.6	3.1	-4.0	-9.7	-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

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 *orto*-, *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 4). 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)** where an oxygen atom from the NO_2^+ electrophile engages the electron-deficient boron atom. In B-substituted 1,2-azaborines, this intermediate lies at slightly higher energies than the regular σ–complex **(1a)**. However, in 1,2-azaborines lacking any substituent in the boron atom it lies a few kcal.mol^{-1} below **(1a)**. In these cases, loss of the boron-bound H^+ leads to an electronic rearrangement which 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 Supporting information) than the corresponding C_3-nitrated analogs

obtained through loss of H^+ from **(1a)**, and further increase the range of molecular scaffolds available from these interesting aromatic compounds.



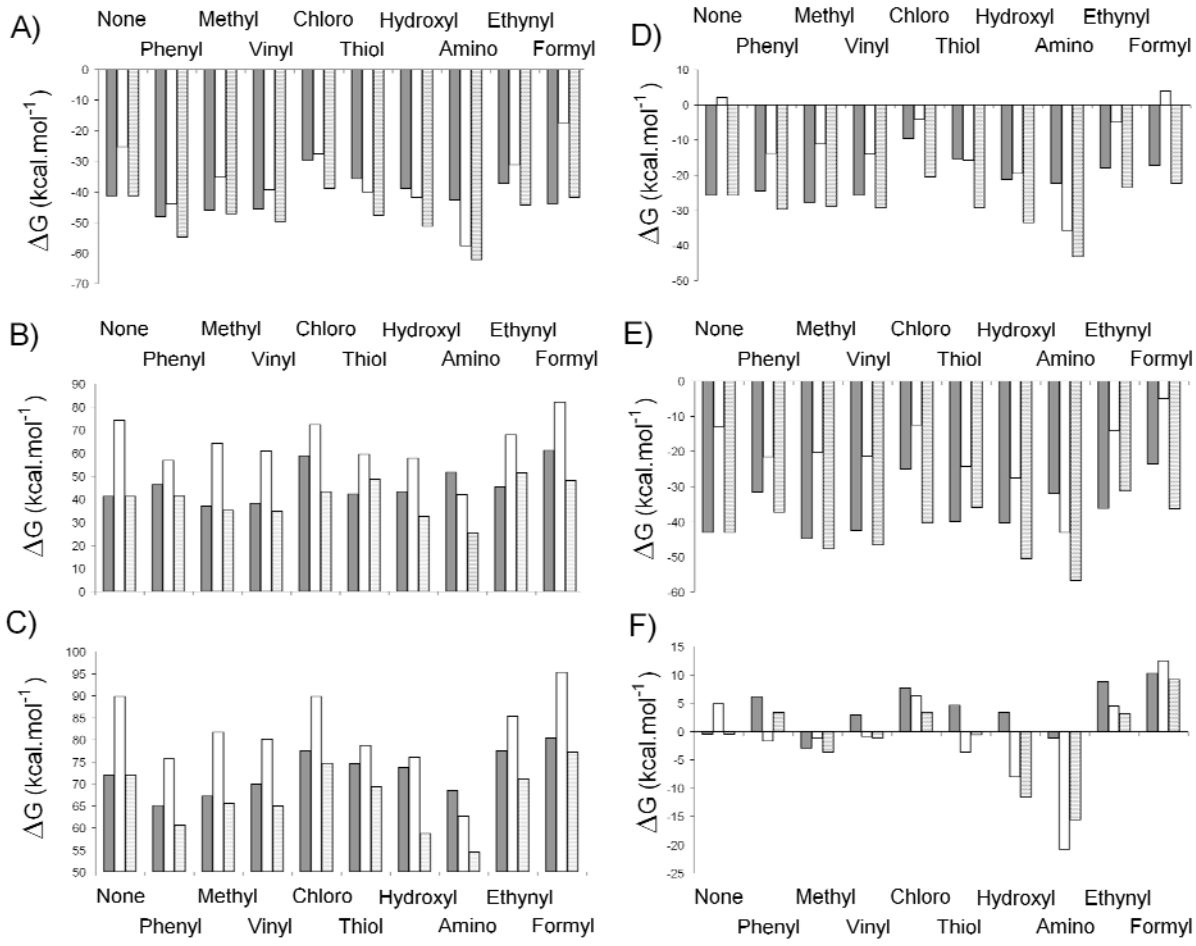


Figure 1: Gas phase (A-C) and solution (D-F) free energies (relative to isolated reactants) of the most stable Wheland intermediates in nitration (A/D), chlorination (B/E), and acylation (C/F) of substituted benzenes (white bars), N-substituted 1,2-azaborines (grey bars) and B-substituted 1,2-

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.

In the corresponding benzene derivatives, nitration is known to be consistently favored on the *orto-* 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 1A). The effect of substitutions on the reactivity of the 1,2-azaborines is generally less dramatic than 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.

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. In order 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[22,23,24]. Analysis of the natural electron populations on the ring atoms (see 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 is negligible (<0.01 e^-), and is 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 *orto-*

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.

Table 4: Computed free energies (in dicloromethane solution) of the nitration reactions (NO_2^+ + R → RNO_2^+) of 1,2-azaborines derivatives (in kcal.mol^{-1}). 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.

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

Chlorination

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 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 5), and therefore the reaction may afford a mixture 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 2), 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 halogenation of the ***carbon*** atoms of 1,2-azaborines is only feasible on boron-substituted 1,2-azaborines.

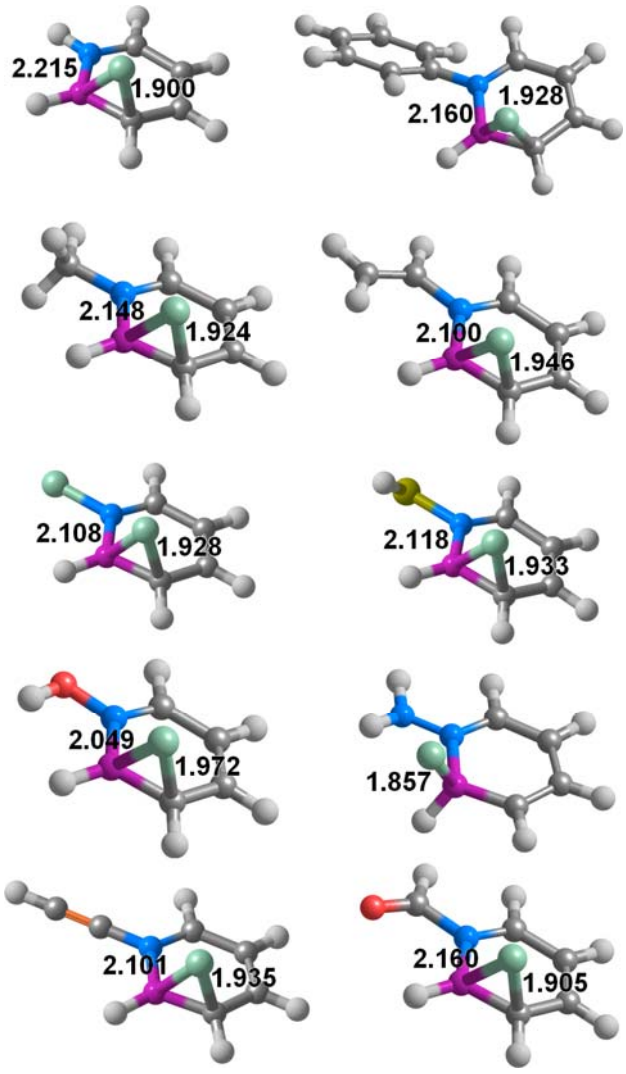


Figure 2: Gas phase geometries of the intermediates arising from Cl^+ addition to the C_3 atom in N-substituted 1,2-azaborines. B-Cl and C_3-Cl distances (in Å) are shown. Substitutents bound to the nitrogen atom are (from left to right, and from top to bottom): H, phenyl, methyl, vinyl, Cl, SH,OH, NH_2,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

Table 5: Computed free energies (in dicloromethane solution) of the chlorination reactions ($FeCl_3$ + Cl_2 + R → $FeCl_4^-$ + RCl^+) of 1,2-azaborines derivatives (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.[a]: intermediate bound on boron, rather than on C_3.

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)[a]	-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

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 unfavourable (ΔG=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 (ΔG=6.4 kcal.mol^{-1}).

The gas-phase stability of the Wheland intermediates formed upon acylation of substituted 1,2-azaborines (Table 6) broadly follows the trends reported above for nitration and chlorination reactions: C_3-bound intermediates are favored (by 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 3) 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 3). 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.

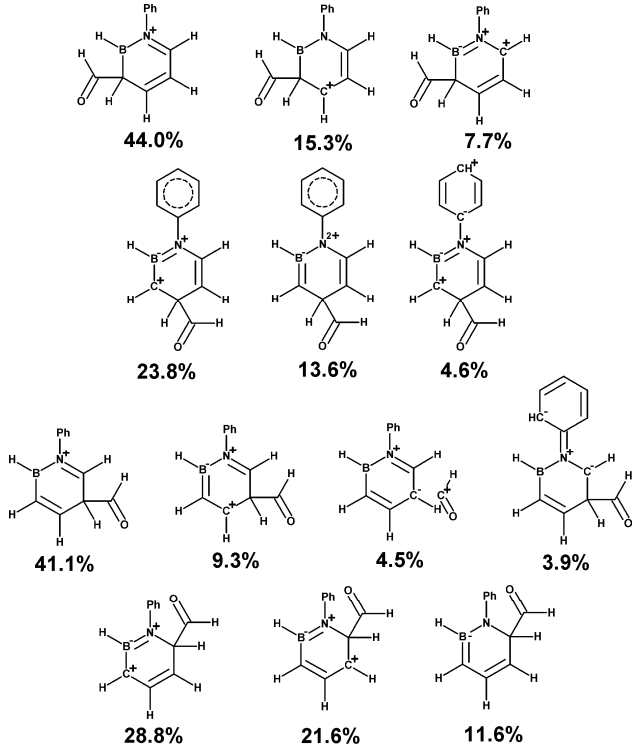


Figure 3: Most-important contributing resonance structures for the σ–complexes formed from addition of formyl cation to 1-phenyl-1,2-azaborine , as computed by Natural Resonance Theory.

Table 6: Computed free energies (in dicloromethane solution) of the acylation reactions ($FeCl_3$ + HCOCl + R → $FeCl_4^-$ + $HCOR^+$) of 1,2-azaborines derivatives (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.

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

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 (Fig. 4). 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 7) were found to be the smallest among the electrophilic substitution reactions we studied (often only a couple of kcal.mol^{-1}) 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'-dimethyl-methyleneiminium 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.

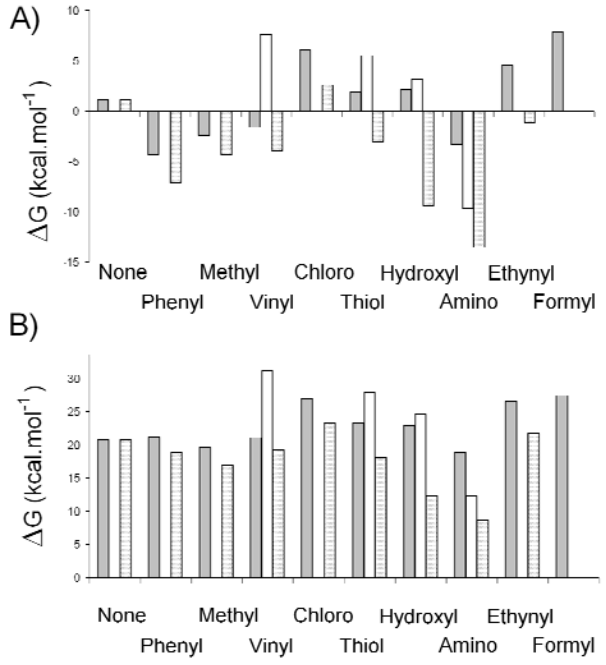


Figure 4: Gas phase (A) and solution (B) free energies (relative to isolated reactants) of the most stable Wheland intermediates in methyleneiminium cation addition to substituted benzenes (white bars), N-substituted 1,2-azaborines (grey bars) and B-substituted 1,2-azaborines (dotted bars).

Table 7: Computed free energies (in gas phase and in dichloromethane solution) of the reactions of 1,2-azaborines derivatives with methyleneiminium cations (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.

	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)				

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.

Supporting information

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). Most-important resonance structures contributing to the computed electron densities of substituted benzenes and 1,2-azaborines, as predicted by Natural Resonance Theory.

Acknowledgments

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

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