J. Phys. Chem. A **2006,** *110,* 1295−1304 **1295**

Coordinate Covalent C → B Bonding in Phenylborates and Latent Formation of Phenyl Anions from Phenylboronic Acid[†]

Rainer Glaser* and Nathan Knotts

Department of Chemistry, University of Missouri−Columbia, Columbia, Missouri 65211

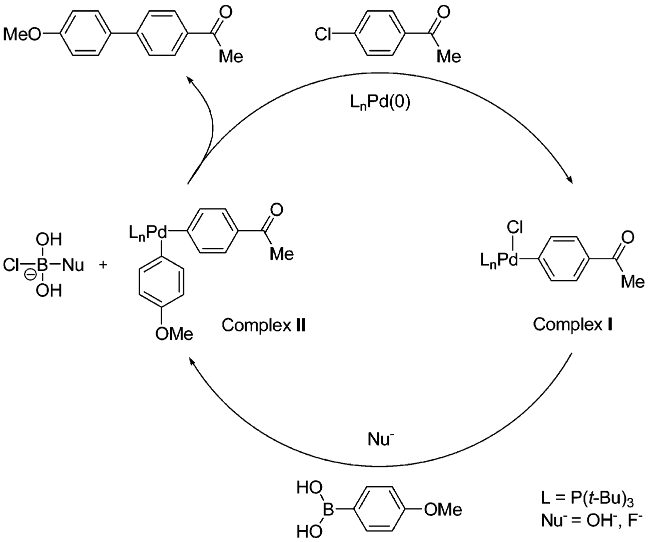
Received: July 4, 2005; In Final Form: August 8, 2005

The results are reported of a theoretical study of the addition of small nucleophiles Nu^- (HO^-, F^-) to phenylboronic acid $Ph-B(OH)_2$ and of the stability of the resulting complexes $[Ph-B(OH)_2Nu]^-$ with regard to Ph−B heterolysis $[Ph-B(OH)_2Nu]^- \rightarrow Ph^- + B(OH)_2Nu$ as well as Nu^-/Ph^- substitution $[Ph-B(OH)_2Nu]^- + Nu^- \rightarrow Ph^- + [B(OH)_2Nu_2]^-$. These reactions are of fundamental importance for the Suzuki−Miyaura cross-coupling reaction and many other processes in chemistry and biology that involve phenylboronic acids. The species were characterized by potential energy surface analysis (B3LYP/6-31+G*), examined by electronic structure analysis (B3LYP/6-311++G**), and reaction energies (CCSD/6-311++G**) and solvation energies (PCM and IPCM, B3LYP/6-311++G**) were determined. It is shown that Ph−B bonding in $[Ph-B(OH)_2Nu]^-$ is coordinate covalent and rather weak (<50 kcal·mol^{-1}). The coordinate covalent bonding is large enough to inhibit unimolecular dissociation and bimolecular nucleophile-assisted phenyl anion liberation is slowed greatly by the negative charge on the borate's periphery. The latter is the major reason for the extraordinary differences in the kinetic stabilities of diazonium ions and borates in nucleophilic substitution reactions despite their rather similar coordinate covalent bond strengths.

Introduction

The Suzuki−Miyaura cross-coupling reaction is an important C(sp^2)-C(sp^2) carbon−carbon bond forming reaction[1−4] with growing significance in laboratory and industrial practice[5] because of its versatility, efficiency, as well as its environmental friendliness.[6,7] The Suzuki−Miyaura reaction consists of the Pd(0)-catalyzed reaction of vinyl or aryl halides with arylboronic acids in the presence of hydroxide or fluoride,[8] and it is illustrated in Scheme 1 for the synthesis of an asymmetrical biaryl.[9] The Pd(0) catalyst is stabilized by phosphine ligands (e.g., PPh_3, $P(t\text{-Bu})_3$).[10] The aryl halide undergoes oxidative addition to the Pd(0) catalyst to form complex **I**, the boronic acid adds a nucleophile to form the reactive tetracoordinated borate adduct, and their reaction results in complex **II**. Product formation via reductive elimination occurs rapidly once both aryls are Pd-coordinated in **II**. The intermediates **I** have been observed in a few instances[11] and the few reports on its formation show a variety of mechanisms to operate.[12,13] The formation of **II** from **I**, that is the replacement of the Pd−X bond in **I** by a Pd−Ph bond, is not well understood in that neither the nature of the reactive borate species has been characterized nor has its reaction with **I** been studied in any detail. The transfer of a phenyl anion from the borate to the Pd(0) complex is the essential event, and one important question in this context is just how easily available phenyl anions are under these conditions. In other words, one should develop a conceptual understanding as to how phenyl borates compare and contrast with organometallic phenyl anion sources, that is, Grignard reagents,[14] Grignard-type reagents,[15] and organolithium reagents[16] in particular. Phenyllithium has a 50-year history[17] and its bonding, ion pairing,[18,19] and aggregation behavior[20−23] have been well studied.

SCHEME 1. Mechanism of the Suzuki−Miyaura Cross-Coupling Reaction of Phenylboronic Acid and Aryl Halides



In this paper, we report the results of a study of the addition of small nucleophiles (HO^-, F^-) to phenylboronic acid and of the stability of the resulting complexes $[Ph-B(OH)_2Nu]^-$ with regard to decomposition by way of phenyl anion formation; eqs 1 and 2 in Scheme 2. We will show that the equilibrium of the Nu^-/Ph^- exchange reaction eq 4 lies on the right. Under typical conditions for the Suzuki−Miyaura reaction (i.e., 2 M aqueous Na_2CO_3, NaF in dry THF solution), the nucleophile concentration allows for the conversion of borane $B(OH)_2Nu$ to $[B(OH)_2Nu_2]^-$ anion, eq 3, and shifting equilibrium 4 to 5, the

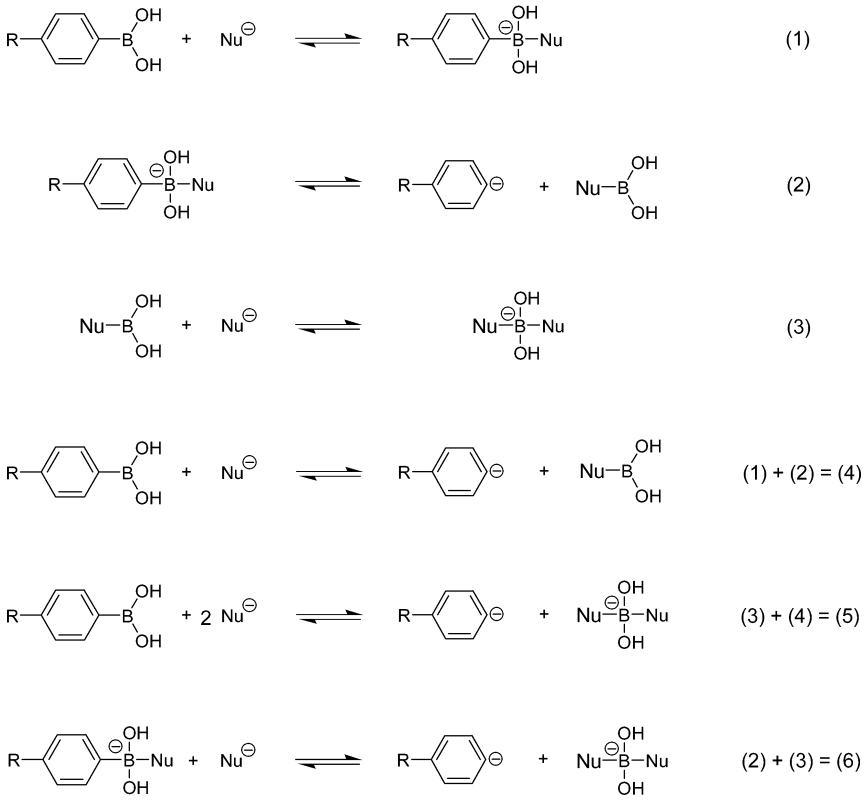
---

* Corresponding author. Email: glaserr@missouri.edu.

[†] Part of the special issue "William Hase Festschrift".

10.1021/jp053658d CCC: $33.50

SCHEME 2. Formation and Decomposition of Borate Anions



reaction of phenylboronic acid with two nucleophiles to form phenyl anion and borate anion. Finally, and most importantly, equilibrium 6 measures the propensity for Nu^-/Ph^- substitution in the borate ions. We begin with the discussion of reaction 3 for boronic acid and fluoroboronic acid to provide a foundation on which to discuss, evaluate, and assess the results for phenylboronic acid.

The results of this study will be relevant to the Suzuki−Miyaura cross-coupling chemistry to synthesize biaryls, as well as heteroaromatic analogues,[24] and they will also inform a variety of related areas of chemistry and biology. The Suzuki carbonylation for the synthesis of diaryl ketones shares common elemental steps,[25] and the recently described homocoupling of phenylboronic acid[26] is thought to involve the replacement of phenyl anion in $[Ph-B(OH)_3]^-$ by gold surface-bound oxygen molecules. Evans' synthesis of diaryl ethers,[27] Kelly's synthesis of aryloxiamines,[28] and Larock's synthesis of polyphenylated alkenes[29] involve adduct formation of phenylboronic acid substrates. The essential role of boron in nature[30] is largely due to the reversible formation of diesters by reaction of boronic acids with 1,2- and 1,3-diols (Scheme 3). *cis*-Diols are best and they occur in nature in ribose (ribonucleosides, RNA) and apiose (rhamnogalacturonan-II, plant cell walls). Cross-links result from diester formation on both sides of a borate,[31] and many biopolymers (RNA, sugars, vitamins, etc.) form such cross-links. Phenylboronic acid disrupts this cross-link formation and has been used to investigate borate cross-links in plant physiology.[32] Phenylboronic acids can condense with other binucleophilic substrates and salicylhydroxamic acid, for example, has been used for protein immobilization and it can form adducts as a 1,2- or a 1,4-aminol.[33] The diester formation with sugars has been used to characterize cell surface receptors,[34] to effect covalent coupling of FAD cofactor on electrode surfaces,[35] and to develop sugar sensors[36] (Scheme 3). Mixed diester formation is likely to be the reason for the successful synthesis of 2*H*-chromene derivatives,[37] and the lipase inhibitor activity[38] of phenylboronic acid might be caused by diester formation close to serine.

Computational Methods

Restricted Hartree−Fock (RHF) theory, hybrid density functional method B3LYP,[39,40] and coupled cluster theory with single and double excitations (CCSD)[41] were employed in conjunction with the diffuse-function augmented, polarized basis sets 6-31+G* (abbreviated A) and 6-311++G** (abbreviated B).[42,43] The flexibility provided by the triply split valence basis set and the full polarization of the larger basis set was thought to be important because the reactions involve hybridization changes at boron as well as changes in molecular regions that are crowded with lone pairs and serve both as acceptors and donors of intramolecular hydrogen bonding. Structures were optimized and vibrational frequencies were calculated at the levels RHF/6-31G+G* and B3LYP/6-31+G*. Unless otherwise noted, B3LYP/6-31+G* structures are discussed. Single-point energies were calculated with the 6-311++G** basis set at the levels B3LYP and CCSD and with the B3LYP/6-31+G* structures; these levels are abbreviated B3LYP/B//B3LYP/A and CCSD/B//B3LYP/A.

The conformational analysis is based on B3LYP/6-311++G**/B3LYP/6-31+G* energies (Table 1). Conformational preference energies tend to be well determined at modest levels of treatment so that only small refinements result from going to higher and higher levels of treatment and this is true in the present case. On the other hand, the reliable computation of reaction energies is considerably more demanding and this is particularly true for heterolyses.[44] Complete sets of reaction energies ΔE computed at all theoretical levels employed are provided in Table 2. We also determined energies at several levels of Møller−Plesset perturbation theory (up to fourth-order) and

SCHEME 3. Cross-Links Formed by Borate Diesters with 1,2- and 1,3-Diols and Diesters of Phenylboronic Acid with Diols and Aminols, and Monolayers of FAD that Are Connected on Gold Surfaces by Way of Diesterification Phenylboronic Acid with Glucose

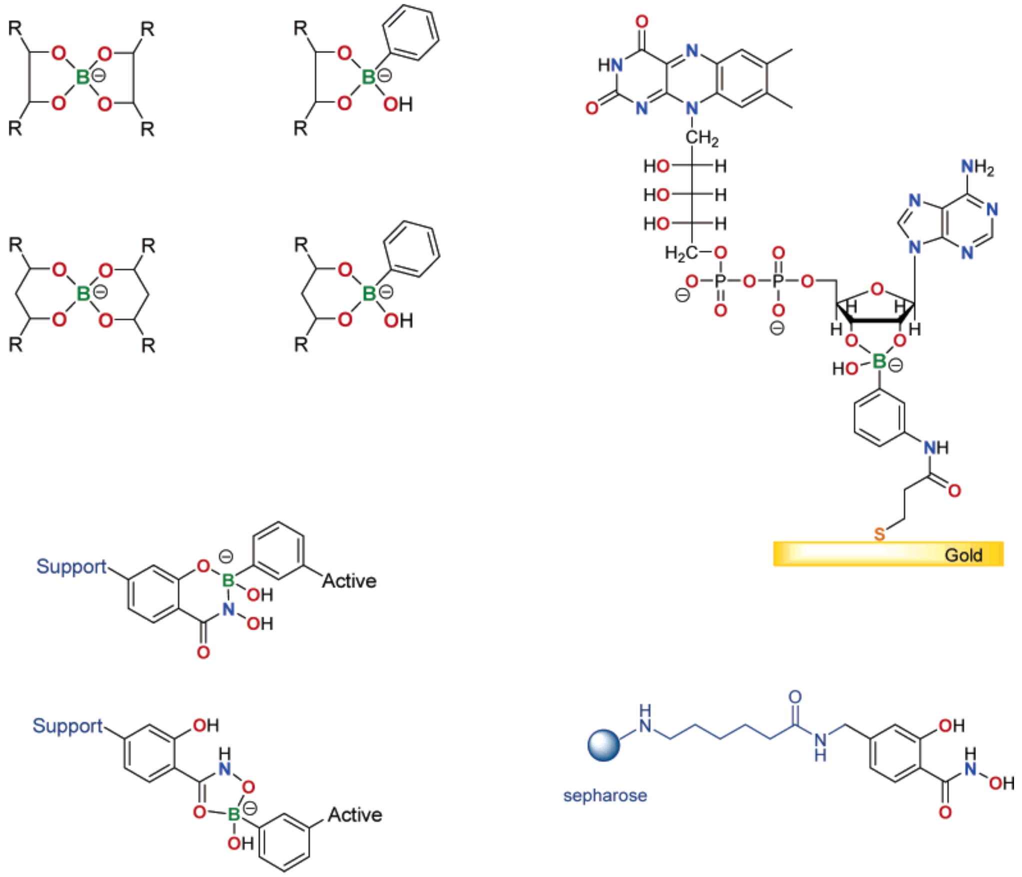


TABLE 1: Conformational Preferences of Boronic Acids[a]

molecule		RHF/A	B3LYP/A	B3LYP/B//B3LYP/A
$B(OH)_3$	**1a**, C_{3h}, vs **1b**, C_s	5.89	5.45	5.06
$F-B(OH)_2$	**2a**, C_s, vs **2b**, C_s	4.66	4.42	4.02
	2a, C_s, vs **2c**, C_s	1.00	0.82	0.73
$Ph-B(OH)_2$	**5a**, C_{2v}, vs **5b**, C_{2v}	6.87	6.09	5.79
	5c, C_2, vs **5d**, C_{2v}	0.90	0.61	0.69
	5c, C_s, vs **5e**, C_{2v}	1.64	1.58	1.52
	5f, C_s, vs **5g**, C_s	4.05	3.78	3.55
	5a, C_{2v}, vs **5f**, C_s	2.01	2.28	2.18
	5b, C_{2v}, vs **5f**, C_s	8.87	8.37	7.97
	5c, C_s, vs **5f**, C_s	3.91	3.46	3.12
	5d, C_{2v}, vs **5f**, C_s	4.80	4.07	3.81
	5e, C_{2v}, vs **5f**, C_s	5.55	5.03	4.64
	5g, C_s, vs **5f**, C_s	4.05	3.78	3.55

[a] Values in kcal mol^{-1}. A: = 6-31+G*. B: = 6-311++G**.

these are reported as well. The CCSD/6-311++G**//B3LYP/6-31+G* calculations (i.e., CCSD/B//B3LYP/A) were performed for the most stable rotamer and/or isomer. Inspection of Table 2 shows significant theoretical level dependencies and corroborate the problems of hybrid density functional theory with heterolyses.[44] In the following the results obtained at the highest level are discussed. In Table 3 are listed the reactions energies, enthalpies, and Gibbs free enthalpies which were computed with the B3LYP/6-31+G* thermochemical data. Solvent effects were determined with the surface polarized continuum (PCM) and the isodensity surface polarized continuum (IPCM) models[45] for water ($\epsilon = 78.39$) and THF ($\epsilon = 7.58$) for both the hydroxide- and the fluoride-catalyzed reactions at the level (I)PCM(B3LYP/B//B3LYP/A).

Electronic structures were examined with the natural bond order (NBO) analysis[46] based on the electron densities computed at the B3LYP/B//B3LYP/A level. Atomic and group charges are summarized in Table 4.

Computations employed Gaussian03 and earlier versions.[47]

Results and Discussion

Boronic Acid, $B(OH)_3$, 1, and Fluoroboronic Acid, $F-B(OH)_2$, 2. C_{3h}-**1a** features $d(BO) = 1.372$ Å and allows for some internal hydrogen bonding with $d(O\cdots H) = 2.438$ Å (Figure 1) in agreement with Gillespie et al.[48] The crystal structure of $B(OH)_3$ contains **1** with near-C_{3h} symmetry[49] and features $d(BO) \approx 1.361$ Å and internal hydrogen bonding with $d(O\cdots H) = 2.386$ Å, as well as intermolecular hydrogen bonding with $d(O\cdots H) = 2.720$ Å. We also determined the structure of conformer C_s-**1b**, which can only realize one internal hydrogen bond with $d(O\cdots H) = 2.396$ Å and is 5.9 kcal mol^{-1} less stable than **1a** (Table 1).

Dewar's AM1 structure[50] of C_s-**2a** features a short bond length $d(BF) = 1.276$ Å and shortened $d(BO)$ bond lengths of 1.348 and 1.360 Å. The semiempirial structure and the RHF and B3LYP structures agree with regard to the BO bond lengths while there is a significant level dependency of the B−F bond length with $d(BF, RHF) = 1.326$ Å and $d(BF, B3LYP) = 1.450$ Å. We also optimized the planar structures **2b** and **2c**; both are minima, and both are less stable than **2a** (Table 1). Two intramolecular hydrogen bonding interactions are possible in **2a** ($O-H\cdots O$ and $O-H\cdots F$) and **2c** ($O-H\cdots F$ twice), and one would reasonably expect **2c** to be more stable than **2a**. It is clear that these attractions are only part of the story, and lone

TABLE 2: Theoretical Level Dependency of Reaction Energies[a]

reaction	RHF/A	B3LYP/A	B3LYP/B// B3LYP/A	MP2/B// B3LYP/A	MP3/B// B3LYP/A	MP4SDQ/B// B3LYP/A	CCSD/B// B3LYP/A
Hydroxide Addition							
1: $PhB(OH)_2 + HO^- \rightarrow PhB(OH)_3^-$	−55.04	−54.03	−52.75	−62.54	−64.63	−62.22	−62.71
2: $PhB(OH)_3^- \rightarrow Ph^- + B(OH)_3$	34.66	40.57	39.82	48.14	45.66	45.96	45.55
3: $B(OH)_3^- + HO^- \rightarrow B(OH)_4^-$	−49.13	−48.82	−47.49	−53.50	−56.07	−53.80	−54.35
4: $PhB(OH)_2 + HO^- \rightarrow Ph^- + B(OH)_3$	−20.38	−13.46	−12.93	−14.4	−18.97	−16.26	−17.16
5: $PhB(OH)_2 + 2\ HO^- \rightarrow Ph^- + B(OH)_4^-$	−71.27	−63.68	−61.82	−67.90	−75.04	−70.06	−71.51
6: $PhB(OH)_3^- + HO^- \rightarrow Ph^- + B(OH)_4^-$	−14.46	−8.25	−7.67	−5.36	−10.41	−7.84	−8.63
Fluoride Addition							
1: $PhB(OH)_2 + F^- \rightarrow PhB(OH)_2F^-$	−41.08	−45.78	−45.48	−52.28	−54.41	−52.41	−52.90
2: $PhB(OH)_2F^- \rightarrow Ph^- + B(OH)_2F$	47.96	52.63	52.20	58.80	57.38	57.38	57.03
3: $B(OH)_2F + F^- \rightarrow B(OH)_2F_2^-$	−46.84	−51.29	−50.94	−54.95	−57.88	−55.55	−56.29
4: $PhB(OH)_2 + F^- \rightarrow Ph^- + B(OH)_2F$	6.88	6.85	6.72	6.52	2.97	4.97	4.13
5: $PhB(OH)_2 + 2F^- \rightarrow Ph^- + B(OH)_2F_2^-$	−39.96	−44.43	−44.22	−48.43	−54.91	−50.58	−52.16
6: $PhB(OH)_2F^- + F^- \rightarrow Ph^- + B(OH)_2F_2^-$	0.65	0.90	0.90	3.85	−0.50	1.83	0.74

[a] Values in kcal mol^{-1}. A: = 6-31+G*. B: = 6-311++G**.

TABLE 3: Computed Reaction Energies[a−c]

reaction	E_{elec}	ΔE_o	ΔE_{298}	ΔG_{298}
Hydroxide Addition				
1: $PhB(OH)_2 + HO^- \rightarrow PhB(OH)_3^-$	−62.71	−61.29	−61.30	−52.56
2: $PhB(OH)_3^- \rightarrow Ph^- + B(OH)_3$	45.55	44.43	43.57	34.03
3: $B(OH)_3 + HO^- \rightarrow B(OH)_4^-$	−54.35	−52.42	−52.57	−44.09
4: $PhB(OH)_2 + HO^- \rightarrow Ph^- + B(OH)_3$	−17.16	−16.86	−17.73	−18.53
5: $PhB(OH)_2 + 2\ HO^- \rightarrow Ph^- + B(OH)_4^-$	−71.51	−69.28	−70.31	−62.62
6: $PhB(OH)_3^- + HO^- \rightarrow Ph^- + B(OH)_4^-$	−8.63	−7.82	−8.84	−9.92
Fluoride Addition				
1: $PhB(OH)_2 + F^- \rightarrow PhB(OH)_2F^-$	−52.90	−47.35	−53.03	−44.42
2: $PhB(OH)_2F^- \rightarrow Ph^- + B(OH)_2F$	57.03	49.46	54.66	42.91
3: $B(OH)_2F + F^- \rightarrow B(OH)_2F_2^-$	−56.29	−56.14	−56.05	−48.03
4: $PhB(OH)_2 + F^- \rightarrow Ph^- + B(OH)_2F$	4.13	2.11	1.63	−1.51
5: $PhB(OH)_2 + 2\ F^- \rightarrow Ph^- + B(OH)_2F_2^-$	−52.16	−54.04	−54.42	−49.53
6: $PhB(OH)_2F^- + F^- \rightarrow Ph^- + B(OH)_2F_2^-$	0.74	−6.68	−1.39	−5.11

[a] Computed at CCSD/B//B3LYP/A. A: = 6-31+G*. B: = 6-311++G**. [b] Values in kcal mol^{-1}. [c] ΔG calculated with $\Delta E \approx \Delta H$.

TABLE 4: Atom and Group Charges

	1a	**2a**	**3**	**4**	Ph^-	**5f**	**6**	**7**	Ph−Li
Li									0.897
B	1.216	1.279	1.147	1.256		1.093	1.025	1.067	
OH	−0.405	−0.385	−0.537	−0.542		−0.381	−0.531	−0.528	
OH	−0.405	−0.405	−0.537	−0.519		−0.393	−0.541	−0.524	
OH	−0.405		−0.537				−0.519		
OH			−0.537						
F		−0.492		−0.586				−0.582	
F				−0.609					
C_{ipso}					−0.400	−0.374	−0.249	−0.265	−0.638
CH_{ortho}					−0.100	0.017	0.005	0.008	−0.080
CH_{ortho}					−0.100	0.017	−0.001	0.004	−0.080
CH_{meta}					−0.142	0.001	−0.056	−0.056	−0.034
CH_{meta}					−0.142	0.001	−0.058	−0.055	−0.034
CH_{para}					−0.116	0.003	−0.075	−0.071	−0.031

pair repulsions (O···O in **1b** and **2c**, O···F in **2a** and **2b**) and μ(HO)−μ(HO) repulsion (notably in **1b** and **2b**) also play important roles.

Structure and Stabililties of $[B(OH)_4]^-$ and $[B(OH)_2F_2]^-$ Anions. Hydroxide ion addition to orthoboric acid forms anion C_2-**3** with d(BO) = 1.487 Å and bond angles ∠(O−B−O) of 115.1 and 106.7° (Figure 2). The BO bond lengthening of ≈0.1 Å in going from $B(OH)_3$ to $[B(OH)_4]^-$ is expected because of the hybridization change at B and the loss of the partial O → B π-conjugation. The anion in the crystal structure[51] of $NaB(OH)_4$ features comparable values: $d(BO)_{average}$ = 1.476 Å, ∠$(O-B-O)_{average}$ = 109.4°, and internal hydrogen bonding distances of about 2.462 Å. In the salt, some of the O atoms are coordinating Na^+ ions as well and much shorter OH···O bond distance of 2.055 Å results.

Addition of fluoride anion to **2** gives C_1-**4** (Figure 2) which features O−H···O and O−H···F internal hydrogen bonds. The B−F bond lengths of 1.430 and 1.461 Å are modestly elongated as compared to **2** and the B−O bond lengths of 1.473 and 1.452 Å are comparable to those in **3**.

The binding energies ΔE_{298} for the addition of hydroxide to **1** and of fluoride to **2** are 52.6 and 56.1 kcal·mol^{-1}, respectively. The HO−B bond formation is less exothermic than the F−B bond formation because **2** is the better electrophile (and *despite* formation of an additional internal hydrogen bond in the formation of **3**). The entropy loss associated with complex

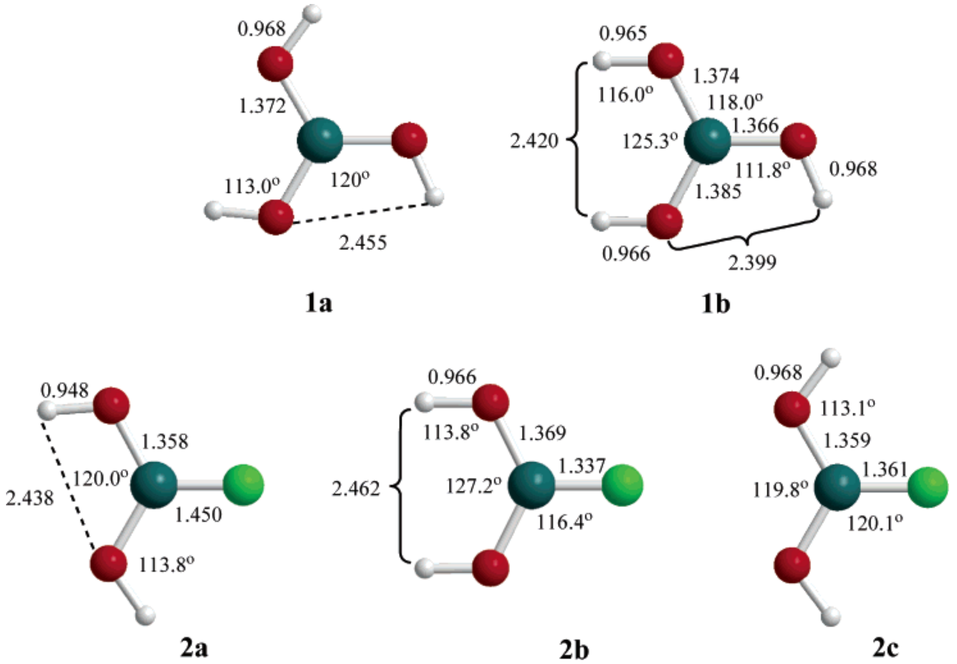


Figure 1. Structures of $B(OH)_3$ and $B(OH)_2F$ (B3LYP/A, Å and deg).

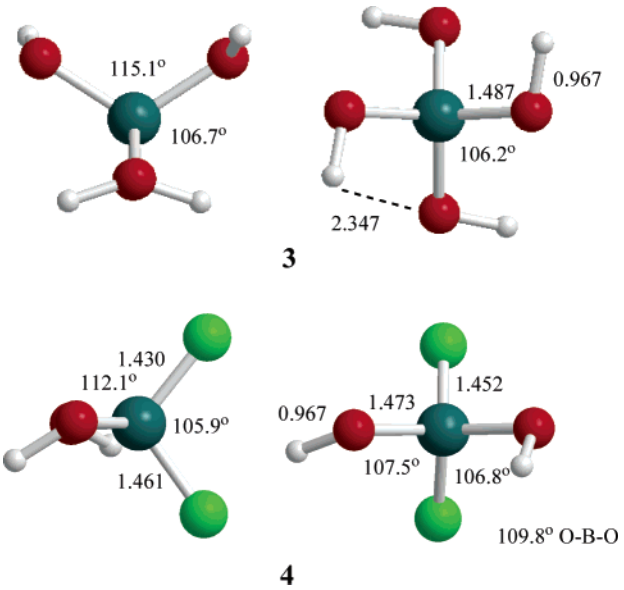


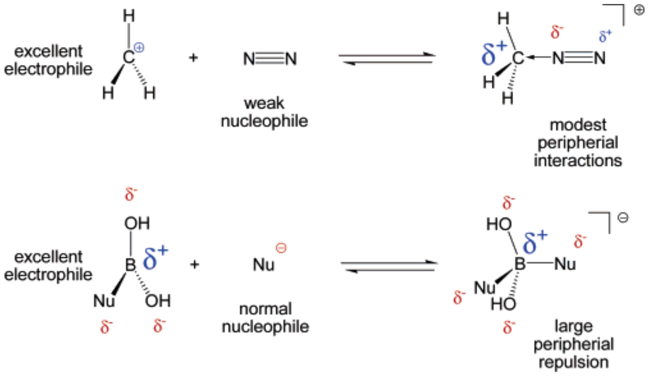
Figure 2. Structures of $[B(OH)_4]^-$ and $[B(OH)_2F_2]^-$ (B3LYP/A, Å and deg).

formation gives corresponding energies ΔG_{298} values of 44.1 and 48.0 kcal·mol^{-1}.

Electronic Structure Analysis of $[B(OH)_4]^-$ and $[B(OH)_2F_2]^-$ Anion Formation. Gillespie's AIM analysis of **1a** showed polar B−O bonds with $q(B) = 2.28$ and $q(OH) = -0.76$ and NBO analysis indicates less bond polarization with $q(B) = 1.21$ and $q(OH) = -0.41$ (Table 4). Both methods show that σ-polarization is extreme and greatly dominates any O → B π-donation. In **2**, fluorine has the highest charge with $q(F) = -0.49$. The boron charge of $q(B) = 1.28$ is about the same as in **1a** and the $q(OH)$ values are slightly smaller (−0.41 and −0.39). The Lewis acids **1** and **2** are rather similar in that they feature a highly positive center surrounded by a highly negative periphery and electronic structures with extreme quadrupole moments result.[52,53]

The addition of hydroxide ion to **1a** increases the oxygen charge by 0.14 in **3** because of the change in the B-hybridization and the impediment of the small O → B π-donation in boronic acid. The addition of fluoride to **2** results in the similar changes of the substituents in **4**. As with the neutral Lewis acids, the anions feature a highly positive center surrounded by a highly negative periphery. Since adduct formation increases the repulsion in the periphery, the complex formation energy is *much lower* than one might expect for a typical bond formation between an anion and what is in essence a cationic B-center.

SCHEME 4. Coordinate Covalent Bonding in Diazonium Ions and in Borate Anions



Coordinate Covalent Bonding in Borate Anions. IUPAC defines "coordination" as the formation of a covalent bond in which the two shared electrons come from one of the two parts of the adduct and coordinate covalent bonding is exemplified by Lewis adduct formation between a Lewis acid and a Lewis base.[54] Coordinate covalent bonds are also referred to as dative bonds (particularly in organic chemistry) and they usually are dipolar bonds. We have been interested in the bonding and the unimolecular dissociation of diazonium ions.[55−57] The C−N bonding in a diazonium ion (Scheme 4) qualifies as coordinate covalent bonding on account of its dissociation behavior (unimolecular heterolysis) as well as the characteristics of the C−N bond (dipolar, semipolar). The definition makes no explicite statement about bond strength but the combination of characteristics imply low bond energies. In Scheme 4, we

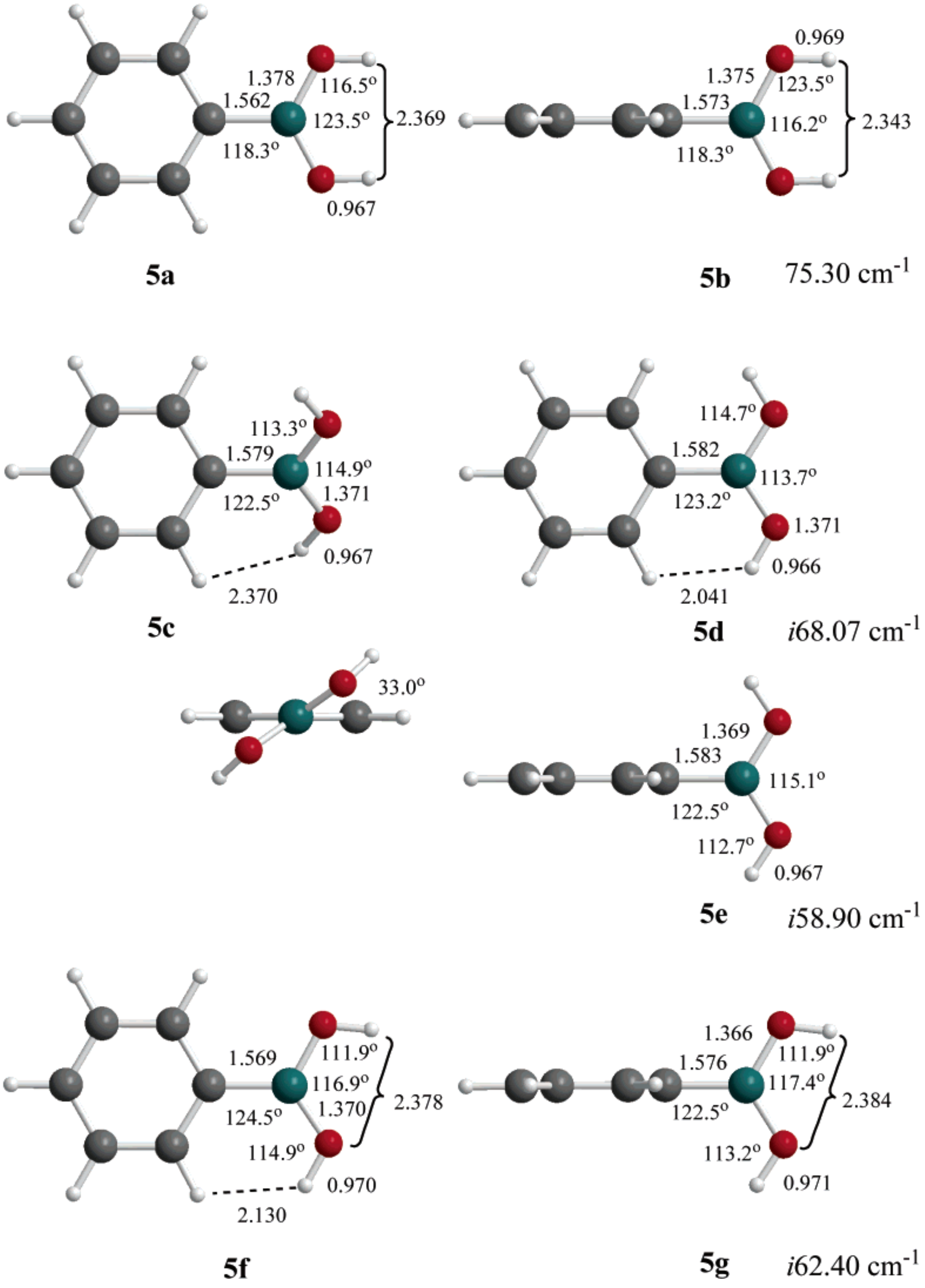


Figure 3. Conformations of phenylboronic acid.

compare and contrast the coordinate covalent bonding in diazonium ions and in borate anions with a view to rationalizing their rather similar bond strengths in these rather different systems (cation vs anion; weak vs strong nucleophile). The large peripheral repulsion in the borate adduct is the major difference and it is the reason for the low binding energy despite the high electrophilicity of the boronic acid and the negatively charged nucleophile.

This conception of the borate formation and dissociation allows for formulations of strategies to moderate B−Nu bonding. B−Nu bonding can be weakened by increasing the peripheral repulsion in the adduct, by stabilization of the nucleophile Nu$^-$, and by reduction of the B-center electrophilicity. We will examine these factors for adducts of phenylboronic acid.

Conformations of Phenylboronic Acid. With regard to the C−O bonds, we considered the conformations cis−cis (**5a** and **5b**), trans−trans (**5c**, **5d**, **5e**), and cis−trans (**5f** and **5g**, Table 1). Structures in which the B(OH)$_2$ and benzene planes are coplanar (or nearly so) are minima and the others are transition state structures for C−B bond rotation and their transition frequencies are provided in Figure 3. Chen et al.[58] reported a preference for trans-cis **5f** at the Hartree−Fock level (RHF/6-31G*) and with molecular mechanics (MM3). We find a preference for **5f** of 2.2 kcal mol^{-1} relative to **5a** and of 3.1 kcal mol^{-1} relative to **5c**. The C−B rotational barriers all are rather small and suggest only minute C → B π-bonding.

Structures and Stabililties of [PhB(OH)$_3$]$^-$ and [PhB(OH)$_2$F]$^-$ Anions. The addition of hydroxide or fluoride, respectively, to **5f** yields ions **6** or **7** (Figure 4). In **6**, the B−O

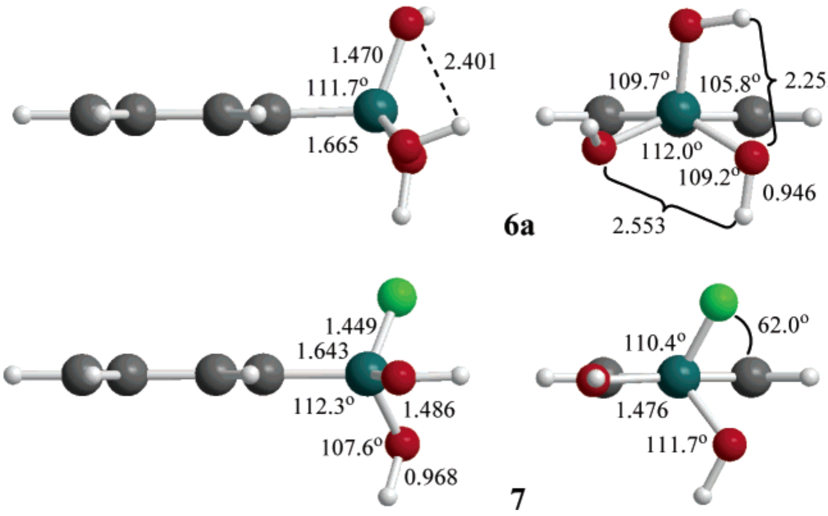


Figure 4. Structures of $[Ph-B(OH)]^-$ and $[Ph-B(OH)_2F]^-$.

bond lengths are 1.470 Å and match the *d*(BO) vlaues in **3**. The OH···O bonds in **6** (2.255, 2.401, 2.533 Å) are as in boronic acid **1a** and its adduct **3**. The B−C bond, already longer than B−O or B−F bonds, increases to 1.665 Å in **6**.

The B−O and B−F bond lengths in ion **7** are similar to those in **4**, and the B−C bond increased notably from 1.577 Å in **5f** to 1.643 Å in **7**. There are two conformational differences between **6** and **7**. One change concerns the B−C conformation; it is staggered in **6** while one C−OH bond and the benzene ring are eclipsed in **7**. The other difference concerns the B−O conformation of the “in-plane” OH group; it is now fully straggered indicating that any OH···F hydrogen bonding is less important than CH_{ortho} avoidance by that hydroxyl group’s O-lone pairs.

For the hydroxide addition to **5f**, we find ΔG_{298}(eq 1, OH^-) = 52.6 kcal·mol^{-1} and there is a notable advantage of *about 8 kcal·mol^{-1}* for hydroxide addition to **5** as compared to **1**, ΔG_{298}(eq 3) = 44.1 kcal·mol^{-1}. On the other hand, for the fluoride addition to **5f** we find ΔG_{298}(eq 1, F^-) = 44.4 kcal·mol^{-1} and a small disadvantage for fluoride addition to **5** as compared to **2a**, ΔG_{298}(eq 3, F^-) = 48.5 kcal·mol^{-1}. As to the relative affinity for adduct formation of **5f**, hydroxide addition to form **6** is preferred over fluoride addition to form **7** by $\Delta\Delta G_{298}$(eq 1, OH^- vs F^-) = 8.2 kcal·mol^{-1}. In contrast, hydroxide addition to **1** is disadvantaged as compared to fluoride addition to **2** by $\Delta\Delta G_{298}$(eq 3, OH^- vs F^-) = 4.4 kcal·mol^{-1}.

With **6** and **7** we can evaluate reaction 2 and our best values for the B−C dissociation energies are ΔG_{298} (eq 2, **6**) = 34.0 and ΔG_{298} (eq 2, **7**) = 42.9 kcal·mol^{-1}. Hence, the phenyl anion dissociation from **6** is preferred over the respective reaction of **7** by $\Delta\Delta G_{298}$(eq 2, OH^- vs F^-) = 8.9 kcal·mol^{-1}. The rather low binding energies indicate that these borate ions indeed are sources of latent phenyl anions and that the nature of the nucleophile used greatly matters to fully exploit this opportunity.

Nucleophile Effect on Propensity for Phenyl Anion Formation. The addition of hydroxide to $Ph-B(OH)_2$ to form **6** (reaction 1) is significantly more exergonic than the addition of phenyl anion to orthoboronic acid to form **6** (reverse of reaction 2) and, consequently, reaction 4 becomes exergonic by ΔG_{298}(eq 2, OH^-) = −18.5 kcal mol^{-1}. This reaction energy is one measure for the propensity of **6** to serve as a source of phenyl anion and it is useful under low nucleophile conditions. The situation is rather different for the fluoride-catalyzed reaction. The addition of F^- to $Ph-B(OH)_2$ (reaction 1) and the addition of Ph^- to **1a** (reverse of reaction 2) are almost isoexergonic and, thus, reaction 4 is almost thermoneutral with a small exergonicity of ΔG_{298}(eq 4, F^-) = −1.5 kcal mol^{-1}. The difference $\Delta\Delta G_{298}$(eq 4, OH^- vs F^-) = 17.0 kcal·mol^{-1} combines $\Delta\Delta G_{298}$(eq 1) = 8.2 and $\Delta\Delta G_{298}$(eq 2) = 8.9 kcal·mol^{-1}.

Under high nucleophile conditions, phenyl anion generation involves Ph−B dissociation of **6** (reaction 2) and hydroxide addition to boronic acid (reaction 3), and we find the combined reaction 6 to be exergonic by ΔG_{298}(eq 6, OH^-) = −9.9 kcal mol^{-1}. Similarly, Ph−B dissociation of **7** (reaction 2) and fluoride addition to fluoroboronic acid (reaction 3) combine to give reaction 6, and this reaction is exergonic by ΔG_{298}(eq 6, F^-) = −5.1 kcal mol^{-1}. The difference $\Delta\Delta G_{298}$(eq 6, OH^- vs F^-) = 4.8 kcal·mol^{-1} combines $\Delta\Delta G_{298}$(eq 2) = 8.9 and $\Delta\Delta G_{298}$(eq 3) = 3.9 kcal·mol^{-1}.

Solvent Effects. We examined solvent effects on reaction 6 with the PCM and IPCM models, the results are similar and documented in the Supporting Information, and we discuss the ICPM data. For the hydroxide reactions in water and THF, we compute solvation corrections of 14.1 and 12.4 kcal·mol^{-1} and, in combination with our best value of ΔG_{298} = −9.92 kcal·mol^{-1}, we obtain $\Delta G_{298}{}^{water}$ = 4.2 and $\Delta G_{298}{}^{THF}$ = 2.4 kcal·mol^{-1}. For the fluoride reactions in water and THF, the solvation corrections are 23.5 and 19.9 kcal·mol^{-1} and in combination with our best value, ΔG_{298} = −5.11 kcal·mol^{-1}, for reaction 6 the energies of $\Delta G_{298}{}^{water}$ = 18.4 and $\Delta G_{298}{}^{THF}$ = 14.8 kcal·mol^{-1} result. See Figure 5 for the surface diagram.

Solvation slows reaction 6 as expected because solvation is better for a small ion (OH^-, F^-) than for a large one (Ph^-). Reaction 6 no longer is exergonic, but it is not very endergonic either and that is all that really matters! It is noteworthy that the solvation energies depend much more on the identity of the small nucleophile than on the identity of the solvent; hydroxide is a much better catalyst than fluoride in both solvents! This result suggests that Suzuki−Miyaura reactions that have been carried out with fluoride-assistance in THF might actually be faster if they were performed with a water-free hydroxide salt in an ether solvent.

Electronic Structure Analysis of $[PhB(OH)_3]^-$ and $[PhB(OH)_2F]^-$ Adduct Formation and Dissociation. The electronic structure of phenylboronic acid **5f** resembles those of boronic acid and fluoroboronic acid: *q*(B) = 1.09 remains above unity and the OH groups carry an average charge of −0.40 as in **1a** (Table 4). The Ph group overall is highly anionic with *q*(Ph) = −0.31 and its internal charge distribution

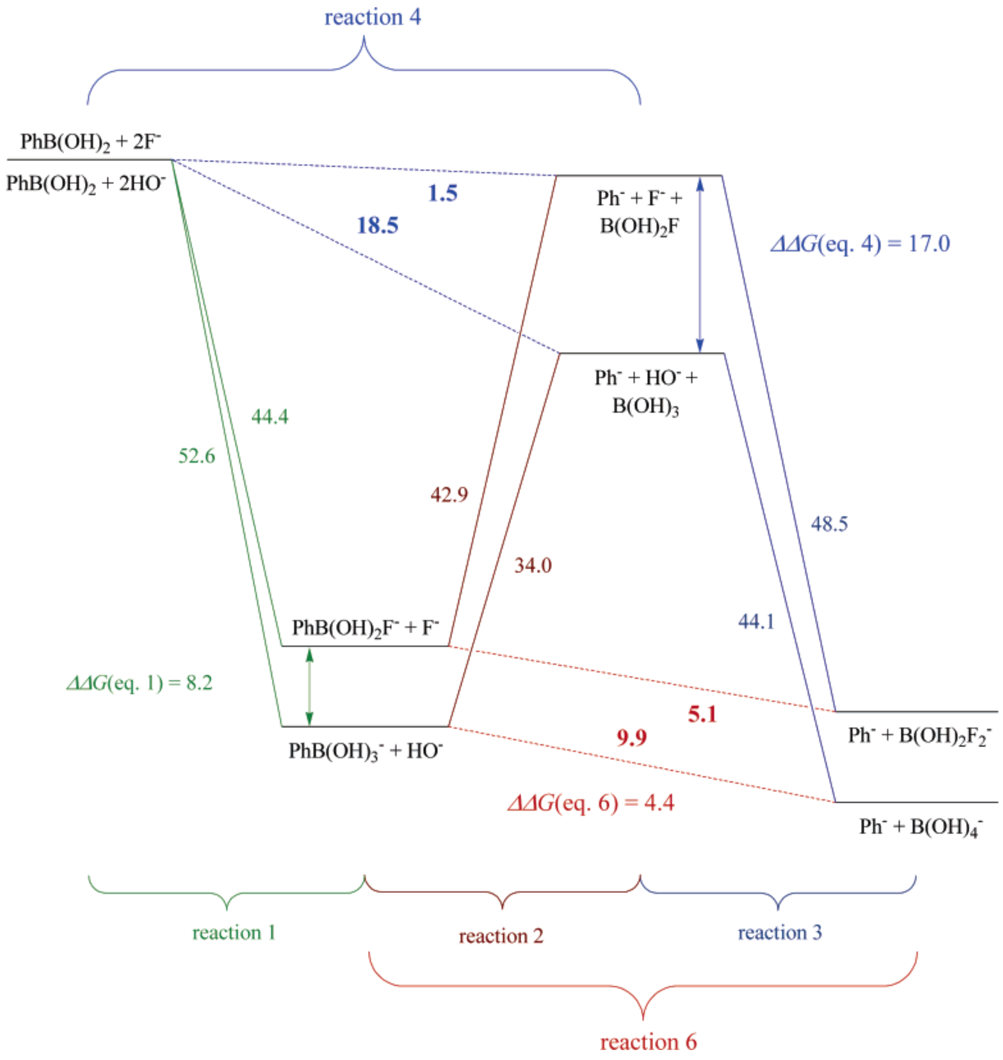


Figure 5. ΔG_{298} surface diagram (kcal mol^{-1}, CCSD/6-311++G**//B3LYP/6-31+G*).

features negative charge localization on the carbon attached to the boron, $q(C_{ipso}) = -0.39$. Hence, the immediate periphery around B is qualitatively the same for the boronic acids X−B(OH)$_2$ with X = F, OH, and C_6H_5. There is however a difference in the degree of the quadrupolarity in that all bonds to B are less polar in **5** than in **1** and **2**. Nucleophile addition to **5** shows an important feature of the phenyl ligand in adducts **6** and **7** as compared to **3** and **4**: While OH and F merely can accumulate charge, the Ph group accumulates and transports charge away from C_{ipso} and thereby achieves a reduction of peripheral repulsion. This bonding situation sharply contrasts with the dominantly ionic bonding in phenyllithium.

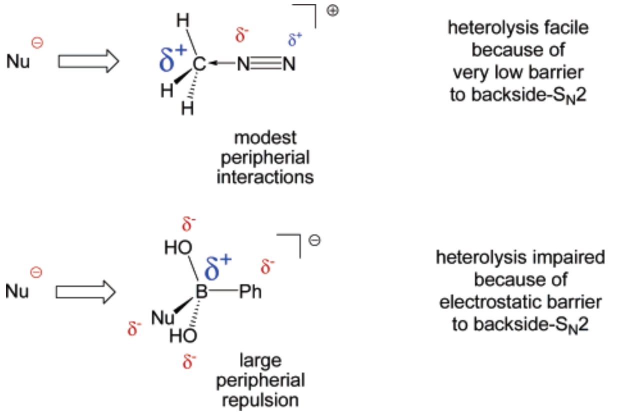
Conclusion

Ion pairing and aggregation reduce the reactivity and the availability for reactions of phenyl anions from sources in which phenyl anion binding is mostly ionic. Phenylborates overcome these disadvantages because phenyl bonding in phenylborates is coordinate covalent and weak. Ion pair formation is not important because of the effective distribution of the negative charge over the large periphery of the borate; and aggregation is no issue.

The small nucleophile-assisted generation of phenyl anion from phenylboronic acid is almost thermoneutral and nucleophile-dependent. The nucleophile dependence is complicated as it reflects the nucleophile's effects on three reactions: (1) its addition to phenylboronic acid, (2) B−C dissociation in the borate adduct, and (3) nucleophile addition to Nu−B(OH)$_2$. The possibilities further increase with the substitution pattern of the phenylboronic acid. The pK_a of phenylboronic acid is 8.8, and the pK_a values of substituted phenylboronic acids vary in the range 4−9.[59] The situation thus is genuinely complex because the various effects cannot be expected to be additive, not even approximately. At the same time, this complexity is responsible for the broad scope of the Suzuki−Miyaura reaction and renders the optimization of each specific system a unique problem.

The study of hydroxide and fluoride was stimulated by experimental practice. The model systems show small endergonicities for the replacement of the phenyl anion in phenylboronic acid by the small nucleophile (reactions 4 and 6). The theoretical study provides a rationale for the long reaction times of typical Suzuki reactions. While weak, the coordinate covalent bonding remains large enough to slow unimolecular dissociation (reaction 2) and the bimolecular phenyl anion liberation reaction also is slowed to the extreme by the negative charge on the periphery. The latter is the major reason for the great differences in the kinetic stabilities of diazonium ions and borates in reactions with nucleophiles (Scheme 5) despite similar coordinate covalent bond strengths. This result leads to the important deduction that C−C coupling in the Suzuki−Miyaura reaction involves the Pd(II) complex **I** and the phenylborate rather than substitution of the Pd(II) complex by a relatively free phenyl anion.

SCHEME 5. Similarity of Coordinate Covalent Bonding Strengths in the Two Cases, While the Kinetic Stabilities toward Nucleophilic Substitution Differ Greatly for the Anion−Cation and the Anion−"Cationic-Center-in-an-Anion" Reactions



Acknowledgment. Some of the calculations were carried out at the National Center for Supercomputing Applications at the University of Illinois, Urbana−Champaign. This research was supported by the UM Research Board, NIH (GM61027) and NSF (DUE-0231354). Dedicated to Bill Hase on the occasion of his 60th birthday.

Supporting Information Available: Tables of total energies, thermochemical data, and Cartesian coordinates of optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595−7598.

(2) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419−2440.

(3) Persichini, P. J. *Curr. Org. Chem.* **2003**, *7*, 1725−1736.

(4) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1329−1469.

(5) Rouhi, M. *Chem. Eng. News* **2004**, *82*, 49−58.

(6) Franzén, R.; Xu, Y. *Can. J. Chem.* **2005**, *83*, 266−272.

(7) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101−2104.

(8) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

(9) (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(10) For use of Pd(II) catalysts, see: Eberhardt, J. K.; Fröhlich, R.; Würthwein, E.-U. *J. Org. Chem.* **2003**, *68*, 6690−6694.

(11) Bei, X.; Turner, W. W.; Weinberg, H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797−6803.

(12) Mechanistic Studies of the Suzuki Cross-Coupling Reaction. Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151−8156.

(13) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944−6945.

(14) (a) *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, R. E., Eds.; Marcel Dekker: 1996. (b) *Grignard Reagents: New Developments*; Richey, H. G., Ed.; John Wiley & Sons: 2000.

(15) Li, C.-J.; Meng, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9538−9539.

(16) Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: New York, 2004.

(17) Gilman, H.; Theodore Soddy, T. *J. Org. Chem.* **1957**, *22*, 1121−1122.

(18) Cuevas, G.; Juaristi, E. *J. Am. Chem. Soc.* **1997**, *119*, 7545−7549.

(19) Kwon, O.; Sevin, F.; McKee, M. L. *J. Phys. Chem. A* **2001**, *105*, 913−922.

(20) Streitwieser, A., Jr. *Acc. Chem. Res.* **1984**, *17*, 353−357.

(21) Reich, H. J.; Goldenberg, W. S.; Sanders, A. W.; Jantzi, K. L.; Tzschucke, C. C. *J. Am. Chem. Soc.* **2003**, *125*, 3509−3521.

(22) Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A.; Bauer, W.; Schleyer, P. v. R. *Organometallics* **1989**, *8*, 1696−1700.

(23) Linnert, M.; Bruhn, C.; Ruffer, T.; Schmidt, H.; Steinborn, D. *Organometallics* **2004**, *23*, 3668−3673.

(24) Dvorak, C. A.; Rudolph, A. A.; Ma, S.; Carruthers, N. I. *J. Org. Chem.* **2005**, *70*, 4188−4190.

(25) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726−4731.

(26) Tsunoyama, H.; Sakurai, H.; Ichikuni, N.; Negishi, Y.; Tsukuda, T. *Langmuir* **2004**, *20*, 11293−11296.

(27) Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029−1032.

(28) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001**, *3*, 139−142.

(29) Zhoum, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765−3777.

(30) (a) Loomis, W. D.; Durst, R. W. *BioFactors* **1992**, *3*, 229−239. (b) Brown, P. H.; Bellaloui, N.; Wimmer, M. A.; Bassil, E. S.; Ruiz, J.; Hu, H.; Pfeffer, H.; Dannel, F.; Römheld, V. *Plant Biol.* **2002**, *4*, 205−223.

(31) (a) Kesavan, S.; Prud'homme, R. K. *Macromolecules* **1992**, *25*, 2026−2032. (b) Wise, E. T.; Weber, S. G. *Macromolecules* **1995**, *28*, 8321−8327.

(32) Bassil, E.; Hu, H.; Brown, P. H. *Plant Physiol.* **2004**, *136*, 3383−3395.

(33) (a) Stolowitz, M. L.; Ahlem, C.; Hughes, K. A.; Kaiser, R. J.; Kesicki, E. A.; Li, G.; Lund, K. P.; Torkelson, S. M.; Wiley, J. P. *Bioconjugate Chem.* **2001**, *12*, 229−239. (b) Wiley, J. P.; Hughes, K. A.; Kaiser, R. J.; Kesicki, E. A.; Lund, K. P.; Stolowitz, M. L. *Bioconjugate Chem.* **2001**, *12*, 240−250.

(34) Otsuka, H.; Uchimura, E.; Koshino, H.; Okano, T.; Kataoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 3493−3502.

(35) Zayats, M.; Katz, E.; Willner, I. *J. Am. Chem. Soc.* **2002**, *124*, 14724−14735.

(36) Takahashi, S.; Anzai, J.-I. *Langmuir* **2005**, *21*, 5102−5107.

(37) Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S. [*sic*]; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467−470.

(38) Raghavendra, M. P.; Prakash, V. *J. Agric. Food Chem.* **2002**, *50*, 6037−6041.

(39) *A Chemist's Guide to Density Functional Theory*, 2nd ed.; Koch, W., Holthausen, M. C., Eds.; Wiley-VCH: Weinheim, Germany, 2001.

(40) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (b) Lee, C.; Parr, R. G. *Phys. Rev. A* **1987**, *35*, 2377−2383.

(41) (a) Raghavachari, K.; Pople, J. A.; Head-Gordon, M. *Lecture Notes Chem.* **1989**, *52*, 215−232. (b) Bartlett, R. J. *Annu. Rev. Phys. Chem.* **1981**, *32*, 359−401.

(42) *Ab Initio Molecular Orbital Theory*; Hehre, W. J., Radom, L., Schleyer, P. v. R., Pople, J., Eds.; Wiley-Interscience: New York, 1986.

(43) *Essentials of Computational Chemistry: Theories and Models*; Cramer, C. J., Ed.; John Wiley & Sons: 2002.

(44) Wu, H.; Glaser, R. *J. Phys. Chem. A* **2003**, *107*, 11112−11119 and references cited there.

(45) (a) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098−16104. (b) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117−129. (c) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327−325. (d) Barone, V.; Cossi, M.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210−3221. (e) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001.

(46) Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 610−627.

(47) Gaussian 03, Revision C.02. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Wallingford CT, 2004.

(48) Gillespie, R. J.; Bytheway, I.; Robinson, E. A. *Inorg. Chem.* **1998**, *37*, 2811−2825.

(49) Zachariasen, W. H. *Acta Crystallogr.* **1954**, *7*, 305−310.

(50) Dewar, M. J. S.; Jie, C.; Zoebisch, E. G. *Organometallics* **1988**, *7*, 513−521.

(51) Csetenyi, L. J.; Glasser, F. P.; Howie, R. A. *Acta Crystallogr. C* **1993**, *49*, 1039−1041.

(52) (a) Wiberg; K. B. *J. Am. Chem. Soc.* **1990**, *112*, 4177−4182. (b) Gobbi, A.; Frenking; G. *J. Am. Chem. Soc.* **1993**, *115*, 2362−2372.

(53) For discussions of an analogous case of a *cation*, see: (a) Glaser, R.; Choy, G. S.-C.; Chen, G. S.; Grützmacher, H. *J. Am. Chem. Soc.* **1996**, *118*, 11617−11628. (b) Glaser, R.; Chen, G. S.; Grützmacher, H. *J. Comput. Chem.* **1997**, *18*, 1023−1035.

(54) IUPAC Recommendations on Organic & Biochemical Nomenclature, Symbols & Terminology etc. http://www.chem.qmul.ac.uk/iupac/.

(55) (a) Glaser, R.; Choy, G. S.-C. *J. Phys. Chem.* **1991**, *95*, 7682−7693. (b) Glaser, R.; Choy, G. S.-C.; Hall, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1109−1120. (c) Glaser, R.; Choy, G. S.-C.; Horan, C. J. *J. Org. Chem.* **1992**, *57*, 995−999. (d) Glaser, R.; Choy, G. S.-C. *J. Am. Chem. Soc.* **1993**, *115*, 2340−2347. (e) Glaser, R.; Horan, C. J. *J. Org. Chem.* **1995**, *60*, 7518−7528.

(56) (a) Glaser, R.; Horan, C.; Nelson, E.; Hall, M. K. *J. Org. Chem.* **1992**, *57*, 215−228. (b) Glaser, R.; Horan, C. J. *Can. J. Chem.* **1996**, *74*, 1200−1214.

(57) (a) Glaser, R.; Horan, C. J.; Zollinger, H. *Angew. Chem.* **1997**, *109*, 2324−2328. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2210−2213. (b) Glaser, R.; Horan, C. J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* **1999**, *64*, 902−913.

(58) Chen, X.; Liang, G.; Whitmire, D.; Bowen, J. P. *J. Phys. Org. Chem.* **1998**, *11*, 378−386.

(59) Yan, J.; Springsteen, G.; Deeter, S.; Wang, B. *Tetrahedron* **2004**, *60*, 11205−11209.