Study of the Dative Bond in 2-Aminoethoxydiphenyl Borate at Various Levels of Theory: Another Poor Performance of the B3LYP Method for B−N Dative Bonds

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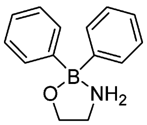
Aminoethoxydiphenyl borate (2-APB), **1**, is a potent inhibitor of store-operated calcium entry channels (SOCCs). Other SOCC inhibitors are being investigated as promising pharmacological agents for a variety of conditions. Though toxic, 2-APB could be useful in the development of additional inhibitors, but its preferred binding structure must first be determined. Thus, we performed ab initio calculations to study the conformers and the strength of the dative bond of 2-APB. As a first step, we performed a series of computations at various levels of theory. We obtained vastly different dissociation energies for the dative bond depending on whether we used MP2 or B3LYP (7−10 kcal/mol different). This discrepancy has previously been observed for other B−N dative bonds by Gilbert, who found that the MP2 values were in much better agreement with experimental values (Gilbert, T. M. *J. Phys. Chem. A* **2004**, *108*, 2550−2554). Since we lacked experimental data for comparison, we performed CCSD(T) calculations and found them to have similar results to those from MP2. Thus, we conclude that MP2 is more accurate for 2-APB. The dissociation free energy at the MP2 level is 7 kcal/mol and indicates that the dative bond conformer will be the predominant structure in the gas phase. The dissociation energy is comparatively low due to the electron donation from the oxygen atom to the boron atom and due to the ring strain in the dative bond conformer.

Introduction

Inhibitors of store-operated calcium entry channels (SOCCs) are being investigated as promising pharmacological agents for a variety of conditions, including malignant transformation, inflammation, and cardiovascular disorders.[1] 2-Aminoethoxydiphenyl borate (2-APB), **1**, is one of the very few inhibitors that are specific to SOCCs.[2] Most other inhibitors that block store-operated calcium channels also have a deleterious effect on other types of calcium channels, such as voltage-gated channels or receptor-operated channels.[3] Unfortunately, 2-APB is toxic to humans and cannot be used as a pharmacological agent. However, it could serve as a model for the development of additional inhibitors specific to SOCCs. With only a few proteins yet identified as SOCCs[4] and no X-ray crystal structures available, this becomes a difficult task and relies heavily on comparison of the structures and electrostatic properties of the inhibitors.



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As a first step in trying to locate more useful inhibitors, we wished to learn more about the conformers and properties of 2-APB using ab initio calculations. Of particular interest is whether the dative bond is necessary for deactivation of SOCCs, since the experimental evidence is inconclusive.[5] Our initial task was to determine an appropriate level of theory for this system. Thus, we performed a series of computations in order to determine the lowest level of theory at which we observed convergence of the B−N dative bond dissociation energy. To our surprise, we obtained vastly different results for B−N dissociation energies from MP2 and B3LYP calculations (Table 1). Gilbert has also observed a similar discrepancy for B−N dative bonds in a variety of other compounds (Table 2).[6] Therefore, we decided to pursue a more in-depth investigation of the relationship between the level of theory and the dissociation energy. We report here on our findings but first provide a brief review of boron−nitrogen dative bond calculations.

Calculations of Boron−Nitrogen Dative Bonds. Boron−nitrogen dative bonds have been studied extensively by quantum calculations,[8] leading to some insights on the effect of the level of theory. First, it is quite clear that correlation energy must be included in any computations.[9] Second, the B−N dative bond appears to be very sensitive to the level of theory and basis set used as the calculated zero-point-corrected dissociation energies for BH_3-NH_3 range from 14 to 32 kcal/mol.[10] Last, as mentioned above, large differences between B3LYP and MP2 calculations can exist. Gilbert found differences in dissociation energies that ranged from 3 to 19 kcal/mol (Table 2),[6] while other groups have found differences of ∼0 to 7.5 kcal/mol.[11] Why the B3LYP and MP2 dissociation energies are similar for some systems but very disparate for others is unclear. Fortunately, Gilbert was also able to compare his results to experimental dissociation energies and found that the MP2 results were in better agreement with experiment than B3LYP or several other DFT methods he tested.[6] However, the MP2-

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TABLE 1: Relative Enthalpies and Free Energies (298 K, kcal/mol) of the Conformers of 2-APB at Different Levels of Theory (Conformer D Contains the Dative Bond)

	ΔH				ΔG			
level of theory	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
RHF/6-31G*	0.0	0.5	0.3	1.8	0.0	0.4	0.8	4.3
B3LYP/6-31+G*	0.4	1.3	1.4	0.0	0.0	0.8	1.2	1.8
B3LYP/6-311+G**//B3LYP/6-31+G*	0.0	1.0	1.0	0.6	0.0	0.7	1.2	2.8
B3LYP/6-311+G**	0.0	1.0	1.0	0.6	0.0	0.8	1.2	2.9
MP2/6-31+G*//B3LYP/6-31+G*	9.9	11.5	9.5	0.0	7.6	9.1	7.5	0.0
MP2/6-31+G*	N/A	11.3	9.5	0.0	N/A	8.5	7.3	0.0
MP2/6-311+G*//MP2/6-31+G*	N/A	10.2	8.5	0.0	N/A	7.4	6.3	0.0

TABLE 2: Comparison of MP2, B3LYP, and CCSD(T)//MP2 B−N Bond Dissociation Energies Corrected for ZPE (6-311++G(d,p) Basis Set, kcal/mol)

complex	exptl[a]	MP2[b]	B3LYP[b]	CCSD(T)	Δ MP2 − B3LYP[b]
BH_3-NH_3	31.1	26.5	23.5	25.5	3.0
BH_3-NH_2Me	35.0	32.3	27.8	31.2	4.5
$BH_3-NH(Me)_2$	36.4	35.6	29.0	34.4	6.6
$BH_3-N(Me)_3$	34.8	36.8	27.8	35.4	9.0
$B(Me)_3-NH_3$	13.8	15.4	6.4	14.4	9.0
$B(Me)_3-NH_2Me$	17.6	20.4	8.7	19.2	11.7
$B(Me)_3-NH(Me)_2$	19.3	22.1	7.0	20.5	15.1
$B(Me)_3-N(Me)_3$	17.6	21.4	2.3	19.2	19.1
ave absolute error		2.6	9.1	2.1	

[a] Ref 7. [b] Ref 6.

calculated bond dissociation energies for the B−N dative bonds were still off by an average of 2.6 kcal/mol.

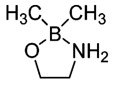
For the most part, it appears that B3LYP and MP2 give similar geometries, and therefore, this is not the reason for the differences between them. The B−N dative bond only varies by 0.04 to 0.05 Å when comparing MP2 and B3LYP geometries.[10a,12] In addition, comparison to crystal structures only gave average errors of 0.04 Å at B3LYP and of 0.02 Å at MP2 for the B−N bond.[6] Giesen and Phillips actually calculated the B−N bond length potential energy surfaces (PES) for CH_3CN-BF_3 at both the MP2 and B3LYP levels of theory and found them to be very similar.[13] Of note was that the PES is very flat from ~1.7 to ~2.6 Å and that the chosen basis set, the inclusion of basis set superposition error (BSSE) corrections, and the inclusion of diffuse functions had a significant effect on the PES. As with Gilbert, the calculated B−N dative bonds were longer than those in the crystal structure.

Methodology

All calculations were completed using the Gaussian98 program[14] or the Gaussian03 program.[15] The calculations were performed using various levels of theory: RHF/6-31G*, B3LYP/6-31+G*, B3LYP/6-311+G**, B3LYP/6-311+G**//B3LYP/6-31+G*, MP2/6-31+G*, MP2/6-311+G**//MP2/6-31+G*, MP2/6-31+G*//B3LYP/6-31+G*, MP2/6-311+G**, and CCSD(T)/6-311+G**//MP2/6-31+G*. Minima were confirmed by the absence of any imaginary frequencies. Established methods were used to calculate the zero-point energies, the thermal corrections, and the entropy contributions for a temperature of 298 K.[16] No scaling factors were employed. For single-point computations, these adjustments were made by employing the frequencies of the optimized geometries used for the energy calculation. Dissociation energies were taken as the relative energy difference between the dative bond conformer and the lowest energy nondative bond conformer. Corrections for BSSE were added using the counterpoise method for the $(OH)H_2B-NH_3$ and $CH_3O(CH_3)_2B-NH_2CH_3$ complexes at the RHF/6-31G*, B3LYP/6-31+G*, and MP2/6-31+G* levels of theory.[17]

Results and Discussion

2-APB is too large a compound on which to perform a full conformational search. So instead, the full search was performed on the smaller 2-aminoethoxydimethyl borate (2-AMB), **2**, and



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the 2-AMB minima were used as starting points for 2-APB optimizations.

2-Aminoethoxydimethyl Borate. Two structural features were used to classify the located minima of 2-AMB. One was the conformation of the aminoethoxy chain and the other was the conformation about the C−N bond. Four possible conformers (**A**−**D**, Figure 1) were located for the aminoethoxy chain at all levels of theory employed. Only one dative bond conformer, **D**, was located. It is in an envelope cyclopentane-type conformation with the CH_2 next to the nitrogen out of plane. The dative bond conformer of 2-AMB has been previously calculated at the HF/6-31G** level of theory.[18] Additional structures involving rotation about the C−N bond were located for **A** and **B** but not for **C** and **D** (see the Supporting Information). These conformers were very similar in energy, and the lowest energy C−N conformers for **A** and **B** were used to calculate the relative energies given in the tables.

For the RHF and B3LYP calculations, the order of the conformers from lowest energy to highest energy is **A** < **B** < **C** < **D**, with an energy difference between **A** and **D** of 2−4 kcal/mol (Table 3). For the MP2 calculations, the order is now **D** < **A** < **B** < **C**, with **D** being preferred by ~4 kcal/mol over **A**. Gilbert's results show that MP2 consistently predicts a more favorable B−N dative bond than B3LYP (Table 2). Our

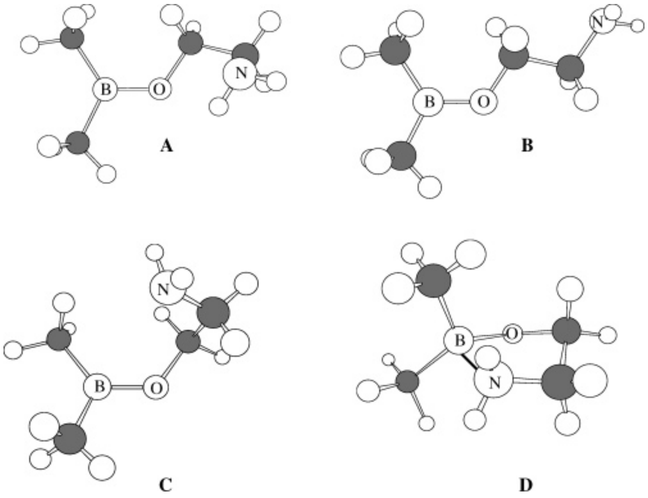

Figure 1. Lowest C−N conformers of **A**, **B**, **C**, and **D** for 2-AMB at the MP2/6-31+G(d) level of theory.

TABLE 3: Relative Enthalpies and Free Energies (298 K, kcal/mol) of the Conformers of 2-AMB at Different Levels of Theory (Conformer D Contains the Dative Bond)

	ΔH				ΔG			
level of theory	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
RHF/6-31G*	0.0	0.8	1.7	4.0	0.0	0.3	1.8	7.0
B3LYP/6-31+G*	0.0	1.3	1.8	2.2	0.0	0.9	2.2	5.4
B3LYP/6-311+G**//B3LYP/6-31+G*	0.0	1.2	1.7	3.2	0.0	0.8	2.1	6.4
B3LYP/6-311+G**	0.0	1.3	1.7	3.3	0.0	0.9	2.3	6.6
MP2/6-31+G*//B3LYP/6-31+G*	4.1	6.1	5.7	0.0	0.9	2.5	2.9	0.0
MP2/6-31+G*	4.2	6.3	5.8	0.0	1.2	3.0	3.1	0.0
MP2/6-311+G**//MP2/6-31+G*	3.5	5.3	5.1	0.0	0.5	2.0	2.4	0.0
MP2/6-311+G**	3.5	5.4	5.0	0.0	0.6	2.2	2.3	0.0
CCSD(T)/6-311+G**/MP2/6-31+G*	2.4	4.1	3.9	0.0	0.0	1.4	1.6	0.5
CCSD(T)/6-311+G**/B3LYP/6-31+G*	2.4	4.1	4.0	0.0	0.0	1.2	1.9	0.7

observations that the B−N conformer is preferred with MP2 but not with B3LYP matches this trend. In addition, our calculated MP2 and B3LYP dissociation energies differ by ∼7 kcal/mol, which is also in accord with Gilbert's previous observations.[6] Examination of the relative free energies shows that the favorability of the dative structure is reduced at all levels of theory (Table 3). This is to be expected since formation of the dative bond introduces a new ring structure, causing a large decrease in flexibility. According to the MP2 and CCSD(T) free energies, the preference for conformer **D** is slight to nonexistent, and we predict that both nondative bond and dative bond structures will be present in the gas phase.

The discrepancy between MP2 and B3LYP is most likely the result of how the different algorithms calculate the energy of the dative bond structure rather than differences in optimized geometries. First, the B3LYP- and MP2-optimized structures are extremely similar except for the B−N bond length (Table 4). Second, for identical geometries, MP2 predicts that the dative bond conformer is most stable, whereas B3LYP predicts that it is the least stable (Table 3, MP2/6-31+G*//B3LYP/6-31+G* and B3LYP/6-31+G*). Last, the MP2/6-31+G*//B3LYP/6-31+G* relative energies are very similar to those of the MP2/6-31+G*-optimized geometries. Even single-point calculations using CCSD(T) do not seem to depend on whether a B3LYP or MP2 geometry is used. Note that the longer bond distance in the B3LYP geometry has no effect when comparing the MP2//B3LYP single-point and MP2//MP2 energies. This supports Giesen and Phillips observation that the B−N bond length PES is very flat.[13]

Since we lack any experimental data for comparison, we decided to perform calculations at a higher level of theory, in particular CCSD(T)/6-311+G**//MP2/6-31+G*, to see whether the B3LYP or the MP2 computations were in better agreement with these presumably more accurate calculations (Table 2). Since CCSD(T) and MP2 are atomic orbital based methods while B3LYP is a hybrid density functional method, it would not be unexpected that the CCSD(T) and MP2 values would end up being closer together. However, the CCSD(T) level of theory has been shown to be very reliable for computing energies for a number of systems,[19] and without experimental data, this is the best comparison available to us. The CCSD(T)/6-311+G**//MP2/6-31+G* dissociation energy lies between the MP2 and B3LYP values and is much closer to the MP2 result (1.1 kcal/mol) than to the B3LYP result (5.7 kcal/mol). This agrees with Gilbert's conclusion that MP2 calculations are more accurate for studying B−N dative bonds.[6]

The above conclusion assumes that CCSD(T) is better able to calculate B−N dissociation energies than MP2. To see whether CCSD(T) is indeed more accurate than MP2, we performed CCSD(T)/6-311+G** single-point calculations on Gilbert's MP2/6-311++G** geometries for which experimental dissociation energies exist. We then compared the CCSD(T)/6-311+G** data to the experimental data (Table 2). The average absolute error for CCSD(T) was not that much better than for MP2 (2.1 vs 2.6 kcal/mol, respectively). Thus, CCSD(T) does

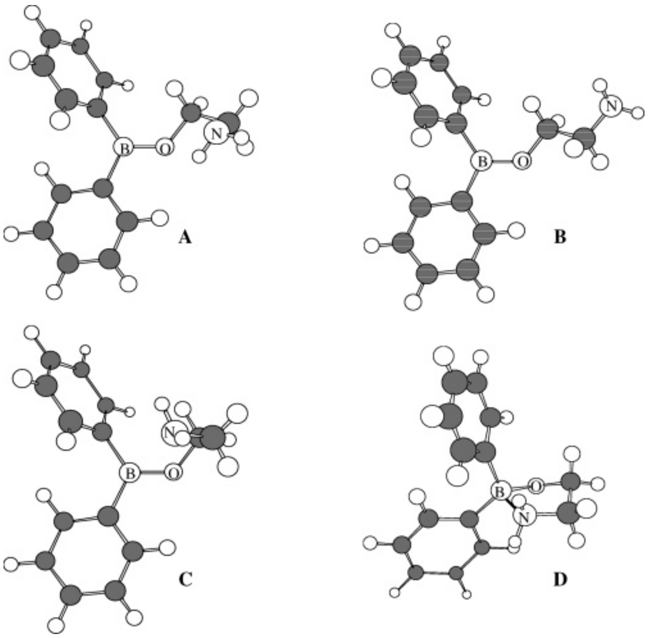

Figure 2. Lowest C−N conformers of **A**, **B**, **C**, and **D** for 2-APB at the B3LYP/6-31+G(d) level of theory.

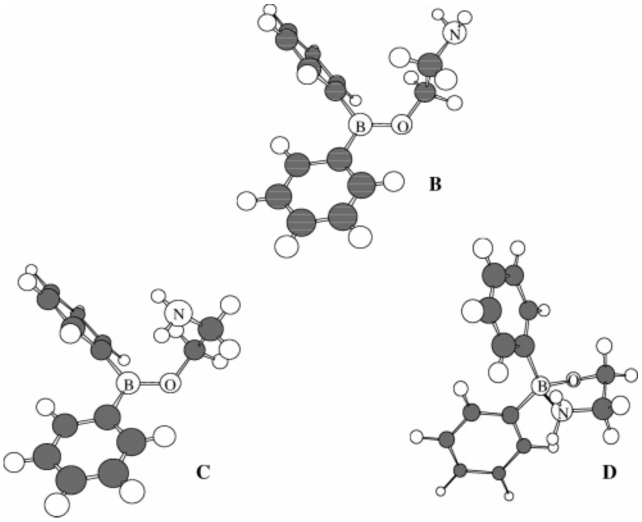

Figure 3. Lowest C−N conformers of **B**, **C**, and **D** for 2-APB at the MP2/6-31+G(d) level of theory.

TABLE 4: Comparison of Geometrical Parameters for 2-AMB at Different Levels of Theory

	A B3LYP/6-31+G*	**A** MP2/6-31+G*	**D** B3LYP/6-31+G*	**D** MP2/6-31+G*
B−O	1.37 Å	1.38 Å	1.47 Å	1.48 Å
O−C	1.43 Å	1.44 Å	1.40 Å	1.41 Å
B−N	N/A	N/A	1.78 Å	1.73 Å
C−N	1.47 Å	1.47 Å	1.50 Å	1.49 Å
O−B−N	N/A	N/A	97.1°	97.9°
B−O−X	123.7°	122.3°	111.1°	109.4°
C−X−N	110.2°	108.9°	103.3°	102.5°
B−N−X	N/A	N/A	104.5°	105.0°
B−O−X−X	172.5°	159.9°	46.9°	47.8°
O−X−X−N	−64.9°	−63.5°	−38.9°	−42.0°
O−B−N−X	N/A	N/A	5.5°	3.5°

TABLE 5: Comparison of Geometrical Parameters for 2-APB at Different Levels of Theory and to the Dative Bond X-ray Crystal Structure[a]

	B B3LYP/6-31+G*	**B** MP2/6-31+G*	**D** B3LYP/6-31+G*	**D** MP2/6-31+G*	exptl[a]
B−O	1.37 Å	1.37 Å	1.46 Å	1.47 Å	1.48 Å
O−C	1.43 Å	1.44 Å	1.40 Å	1.41 Å	1.41 Å
B−N	N/A	N/A	1.77 Å	1.72 Å	1.65 Å
C−N	1.47 Å	1.47 Å	1.50 Å	1.50 Å	1.49 Å
O−B−N	N/A	N/A	97.5°	98.5°	98.4°
B−O−X	127.0°	122.4°	110.7°	108.1°	107.7°
C−X−N	109.2°	108.5°	103.3°	102.6°	105.2°
B−N−X	N/A	N/A	104.4°	104.7°	105.5°
B−O−X−X	141.2°	83.6°	47.3°	49.5°	−39.6°
O−X−X−N	178.8°	179.3°	−38.5°	−41.4°	39.3°
O−B−N−X	N/A	N/A	6.9°	6.9°	3.1°

[a] Ref 20.

not provide a large enough increase in accuracy to offset its much larger computational demands and will not be pursued for 2-APB.

So far, we have focused mainly on the level of theory, but the choice of basis set is also important as previously indicated by Giesen and Phillips.[13] Inspection of our calculated energies with respect to basis set shows that going from a double-ζ split-valence basis set to a triple-ζ split-valence basis set has a significant effect on the relative energies. However, this is not the result of differences in geometries as MP2/6-311+G**//MP2/6-31+G* gives the same dissociation energy as MP2/6-311+G** optimizations. For this reason, and because MP2/6-311+G** optimizations require so much more computational resources, only MP2/6-311+G** single points will be performed for 2-APB.

2-Aminoethoxydiphenyl Borate. As mentioned above, the 2-AMB minima were converted to 2-APB structures by replacing the methyl groups with phenyl groups and reoptimizing. The conformers of the aminoethoxy chain and C−N rotation located for 2-APB at the RHF and B3LYP levels were very similar to those of 2-AMB (Table 1, Figure 2, and the Supporting Information). However, at the MP2 level of theory, there is a significant change in the potential energy surface (Table 1, Figure 3). Conformer **B** now has a bend in the aminoethoxy chain instead of being completely extended. In addition, structure **A** is no longer a minimum on the PES and two new C−N conformers for structure **C** were located. The relative order is now **D** < **C** < **B,** and the relative energy between conformers **C** and **D** will be used as the dissociation energy.

Again, a large discrepancy between the B3LYP and MP2 relative energies is observed, with essentially no preference between conformers **A** and **D** for B3LYP and a preference for conformer **D** over **C** of 9−10 kcal/mol for MP2. Thus, the difference in BDE between B3LYP and MP2 has increased to ∼10 kcal/mol for 2-APB. The MP2 single points on the B3LYP geometries again show that this is not a result of a difference in geometry, as does a comparison of the structures optimized at the different levels of theory (Tables 1 and 5). Again, the longer B−N bond in the B3LYP structure has almost no effect on the MP2 single-point relative energies. The inclusion of entropy reduces the MP2 dissociation free energy by ∼2 kcal/mol, but it is still significant at 6 kcal/mol (Table 1). Thus, the dative bond conformer should be the predominant structure in the gas phase.

An X-ray crystal structure of the dative bond conformer of 2-APB is also available for comparison.[20] The bond lengths and angles of the B3LYP and MP2 dative bond conformers are in good agreement with those of the X-ray structure (Table 5). The five-membered rings in the X-ray structure and conformer **D** are enantiomeric, giving dihedral angles of opposite signs, but which are otherwise within 10° of each other. Both structures are envelopes with the same CH_2 group out of plane. An X-ray structure with the oxygen atom out of plane also exists, but we could not locate this conformer at any level of theory. In agreement with previous observations, our calculated dative bond is longer than that in the X-ray structure. Particularly since the energy of the dative bond is not very dependent on its length,[13] we are not concerned by the small disagreements between MP2 and X-ray.

Comparison of 2-AMB and 2-APB. The above results show that the conformer containing the boron−nitrogen dative bond is only slightly preferred for 2-AMB but strongly favored for 2-APB. Thus, the replacement of the methyl groups with phenyl groups strengthens the dative bond. Normally, electron-donating groups on boron will make it a worse Lewis acid, weakening the dative bond, while electron-withdrawing groups have the opposite effect. Phenyl groups are supposed to be electron donating through π-bond resonance. Therefore, the strength of the dative bond in 2-APB is expected to be similar to that of

TABLE 6: Bond Dissociation Energies (kcal/mol, 298 K) of BH_2OH-NH_3 and $(CH_3)_2BOH-NH_2CH_3$ at Different Levels of Theory (Energies Corrected for Basis Set Superposition Errors Are in Parentheses)

level of theory	BH_2OH-NH_3 ΔH	$(CH_3)_2BOH-NH_2CH_3$ ΔH
RHF/6-31G*	4.1 (1.1)	−0.1 (−3.9)
B3LYP/6-31+G*	8.6 (6.3)	2.3 (0.3)
B3LYP/6-311+G**//B3LYP/6-31+G*	7.0	1.1
B3LYP/6-311+G**	7.1	1.1
MP2/6-31+G*//B3LYP/6-31+G*	11.5	12.4
MP2/6-31+G*	11.6 (5.5)	12.8 (3.7)
MP2/6-311+G**//MP2/6-31+G*	10.4	11.8
MP2/6-311+G**	10.3	11.8
CCSD(T)/6-311+G**/MP2/6-31+G*	9.7	10.6

2-AMB, which has electron-donating methyl groups. However, due to steric hindrance, both phenyl rings cannot occupy the plane of the boron σ-bonds at the same time and one must twist out of plane (Figure 3). This prevents any electron donation from the π-molecular orbitals of the twisted benzene ring to the empty p-orbital of the boron atom. Instead, the phenyl groups acts as a σ-bond electron-withdrawing group and stabilizes the dative bond. This same effect was also observed for calculations on boron radicals with methyl and phenyl substituents.[21]

Effect of a B−O Covalent Bond on a B−N Dative Bond. In our calculations for 2-AMB, the dissociation energy of the dative bond is 3.5 kcal/mol and for 2-APB, 8.9 kcal/mol; yet the dissociation energies for the systems studied experimentally range from 14 to 36 kcal/mol.[7] There are two factors which could account for the weaker dative bonds in our systems. The first is increased sterics from the cyclopentane ring in the dative bond conformer. Using Bachrach's group equivalent method,[22] we calculate a ring strain energy of 7.6 kcal//mol, which is slightly larger than the ring strain energy of cyclopentane (6.2 kcal/mol)[23] (details in the Supporting Information).The second possible factor is the substituent effect of the electron-donating oxygen bonded to the boron atom. Numerous experimental systems exist which demonstrate the deleterious effect a B−O bond has on B−N dative bond strength.[24]

To better quantify the effect of the oxygen atom on the dissociation energies, we performed calculations on two model systems, $(HO)H_2B-NH_3$, **3**, and $CH_3O(CH_3)_2B-NH_2CH_3$, **4**, which has the same substitution pattern as 2-AMB (Table 6). For **3**, the dissociation energy is 7.1 kcal/mol at B3LYP, 10.3 kcal/mol at MP2, and 9.7 kcal/mol at CCSD(T), while for **4**, it is 1.1 kcal/mol at B3LYP, 11.8 kcal/mol at MP2, and 10.6 kcal/mol at CCSD(T). As with 2-AMB and 2-APB, the CCSD(T) values lie between the B3LYP and MP2 values and are closer to the MP2 values.

Surprisingly, the MP2−B3LYP difference jumps from ∼3 kcal/mol to ∼11 kcal/mol on going from **3** to **4**. Therefore, the MP2 and CCSD(T) results predict that the two systems have similar dissociation energies, while B3LYP predicts that **3** should have a much stronger dative bond than **4**. Apparently, the addition of the methyl groups causes B3LYP to perform even more poorly. In his paper, Gilbert also noted that the addition of each CF_3 group to boron increased the difference between MP2 and B3LYP.[6] Reexamination of his data shows that the addition of methyl groups to either the boron or nitrogen atoms also increases the discrepancies between MP2 and B3LYP, with BH_3-NH_3 having the smallest difference of 3 kcal/mol (Table 2).

Comparison of the dissociation energies of BH_3-NH_3 (experimental) and **3** (calculated) shows that **3** has a weaker dative bond by 21 kcal/mol. Thus, the presence of the oxygen atom does contribute to the lower dissociation energies of 2-AMB and 2-APB. However, comparison of **4** and 2-AMB indicates that 2-AMB has a weaker dative bond by 8 kcal/mol despite the fact that both have the same substitution pattern. This value is remarkably similar to the strain energy calculated above. Therefore, we believe that the increased sterics associated with formation of the five-membered ring and dative bond also contributes to the lower dissociation energies of 2-AMB and 2-APB. In summary, both factors are important, but the oxygen clearly has a larger effect.

Basis set superposition error corrections were included for calculations performed with smaller basis sets, since studies have shown that inclusion of BSSE via the counterpoise method does not improve the agreement between calculated values and experimental ones for larger basis sets.[25] The BSSE corrections were 3−4 kcal/mol for RHF, ∼2 kcal/mol for B3LYP, and 6−9 kcal/mol for MP2 (Table 6).

Conclusion

We have presented additional data highlighting the poor performance of B3LYP for B−N dative bonds. We observed differences of 7, 10, 3, and 11 kcal/mol between MP2 and B3LYP dissociation energies for our systems, 2-AMB, 2-APB, $(HO)H_2B-NH_3$, and $CH_3O(CH_3)_2B-NH_2CH_3$, respectively. The accuracy of the B3LYP level of theory is system dependent, based on our and others' work, and seems to worsen with increasing methyl substitutions. However, MP2 calculations seem to give fairly good results when compared to experiment[6] or CCSD(T) calculations. We have also confirmed that B−N dative bond calculations are very sensitive to the method used and the choice of basis set, with at least a triple-ζ split-valence basis set being required to get the most accurate dissociation energies. Thus, we will use the MP2/6-311+G**//MP2/6-31+G* level of theory for all future calculations on systems containing B−N dative bonds, with the awareness that these numbers are probably off by ∼2.5 kcal/mol.

As for 2-AMB and 2-APB, we predict that 2-AMB has no preference for the dative bond conformer in the gas phase, though this structure is probably present. For 2-ABP, the dative bond conformer is strongly preferred and is probably the only structure present in the gas phase. This strongly suggests that 2-APB binds to SOCCs in the dative bond conformer, especially since higher dielectrics should only further stabilize the dative bond. However, solvent studies will need to be performed to confirm this. 2-APB has the stronger dative bond because one of the phenyl rings is twisted out of plane and acts as an electron-withdrawing group. Overall, the dative bonds of 2-AMB and 2-APB are weaker than those of other systems because of the electron donation of the oxygen atom bonded to boron. The increased strain of the dative bond conformer when compared to other possible conformers also contributes to the weaker dative bond. We plan to continue our studies of 2-APB by adding solvent and substituents to our calculations in the hope of gaining further information that will be useful when designing SOCC inhibitors.

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Supporting Information Available: Total energies for all compounds and relative energies for the conformers of 2-AMB and 2-APB as well as details on calculation of the ring strain for 2-AMB conformer **D**. This material is available free of charge via the Internet at http://pubs.acs.org.

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