Computational Chemistry

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Mechanistic Insights into Direct Amide Bond Formation Catalyzed by Boronic Acids: Halogens as Lewis Bases**

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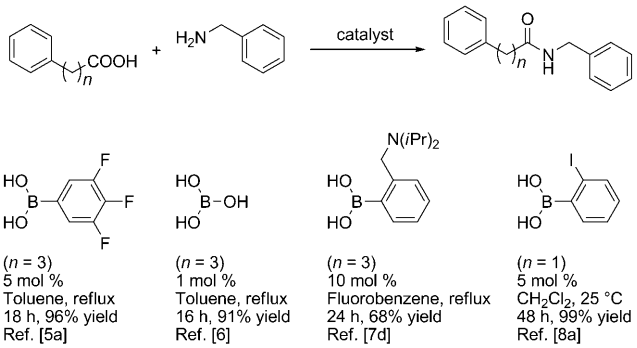
A recent survey among leading pharmaceutical companies conducted by the ACS Green Chemistry Institute identified "amide formation avoiding poor atom economy reagents" as a key challenge in synthetic chemistry.[1] This finding was hardly surprising, considering that roughly one out of twelve reactions in the synthesis of drug candidates is estimated to be the formation of an amide bond.[2] In fact, a study carried out in 1999 showed that about 25% of known pharmaceuticals contained at least one amide bond.[3] In spite of this, direct amide bond formation (the condensation of amines with carboxylic acids yielding water as the sole by-product) is relatively underdeveloped. The significance and limitations of catalytic approaches to amide bond formation[4a] and to condensations in general[4b] have been recently discussed.

In this respect, recent studies from different research groups demonstrated that substoichiometric amounts of boronic acids can efficiently promote direct amide bond formation, provided that water is removed from the reaction mixture (Scheme 1).[5–8] In particular, Hall and co-workers found that using *ortho*-halophenyl boronic acids as catalysts, the coupling reactions can be carried out at room temperature.[8a]

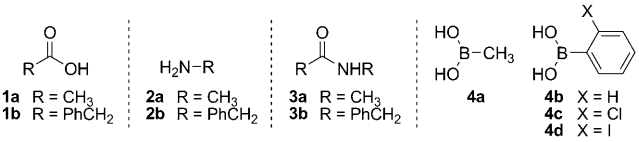
It was proposed that these reactions proceed via formation of a mono-[5a] or diacyloxyboronate species,[7d] which are activated acyl donors capable of reacting with the amine to form the amide product. However, kinetic analysis as well as ESI/MS and ^{1}H NMR studies did not provide sufficient information to unambiguously elucidate the mechanism of this transformation.[7c,d] Also, the superior activity of *ortho*-halophenylboronic acids could not be rationalized.[8a] Starting from the presumption that a detailed mechanistic understanding might provide crucial insights to improve catalyst design and render this approach a practical alternative to stoichiometric coupling reagents, this contribution presents a study of the reaction mechanism using density functional theory.



Scheme 1. Direct amide bond formation catalyzed by boron-based acids.

Herein, geometry optimizations at the B3LYP/6-31G(d,p) level of theory were followed by vibrational analysis and evaluation of solvent effects using the CPCM model for dichloromethane. The final energies of the stationary points were calculated using both B3LYP and MPW1K with the larger 6-311 + G(2d,2p) basis set and corrected for zero-point vibrational effects. For all calculations on iodine-containing structures, the LANL2DZ*dp* basis set was used for the halogen atom.[9] While the final energies obtained with the two methods are in some cases remarkably different, the B3LYP and MPW1K functionals yield the same qualitative results for all the significant issues addressed in this study. In the absence of robust benchmarking data on this type of systems, such a discrepancy between theoretical methods imposes the values reported here to be regarded as indicative of trends in reactivity rather than as accurate representations of the actual energetics for the transformation examined. The energies mentioned in the following discussion are CPCM-corrected MPW1K values. The structures employed in the modeling of the reaction are depicted in Scheme 2.

Several mechanistic possibilities for product formation from substrates **1a** and **2a** with catalyst **4a** were investigated computationally (see the Supporting Information). Pathways involving ionized reactants (acetate **1a′** and methylammonium **2a′**) were found to be more energetically demanding



Scheme 2. Substrates and catalysts used for the calculations.

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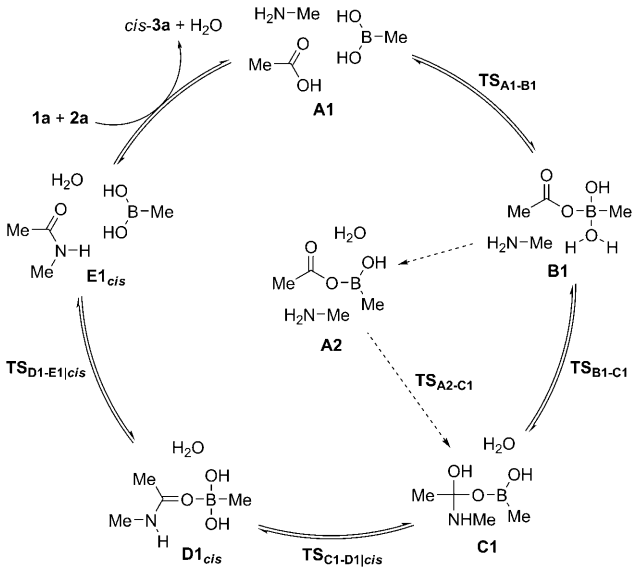
than those involving neutral species. In fact, while aliphatic amines and carboxylic acids readily form salts in water and highly polar solvents, their pK_a order switches in aprotic organic solvents of lower polarity.[4a,10] Reaction sequences containing diacyl boron derivatives were also found to have significantly higher overall barriers. The calculated lowest-energy pathway for the formation of amide **3a** involves generation of a tetracoordinate monoacyl boronate ($\mathbf{TS_{A1\text{-}B1}}$), C–N bond formation ($\mathbf{TS_{B1\text{-}C1}}$), *cis*-selective water elimination from the resulting hemiaminal ($\mathbf{TS_{C1\text{-}D1|}_{cis}$), and amide decomplexation ($\mathbf{TS_{D1\text{-}E1|}_{cis}$; Scheme 3).[11] The structures of selected optimized stationary points are represented in Figure 1.



Scheme 3. Lowest-energy calculated catalytic cycle.

The catalytic cycle begins with the reaction of acid **1a** and catalyst **4a**, which takes place via concerted proton transfer and B–O bond formation ($\mathbf{TS_{A1\text{-}B1}}$). The calculated barrier for this reaction of 7.6 kcal mol^{-1} indicates a very fast process, in contradiction with previous hypotheses on this step being rate determining.[5a,7d] While protonation of the boron-bound OH group is accompanied by a considerable increase in the B–O bond length, the newly generated water molecule is not expelled in this reaction step. The next issue which was addressed in this study is the nature of the acylating species which reacts with the amine. In principle, both tri- and tetracoordinate acyloxy boronates can undergo nucleophilic attack by an amine group. Despite repeated attempts, no first-order saddle point unambiguously corresponding to the formation of **A2** from **B1** ($\mathbf{TS_{B1\text{-}A2}}$) could be located. The energy required for this process was therefore estimated in 1.4 kcal mol^{-1} (B3LYP, gas-phase) by gradually increasing the B–O bond distance starting from structure **B1**. Reaction of the tricoordinate acyl boronate was found to be considerably more demanding than that of its tetracoordinate counterpart, with $\mathbf{TS_{A2\text{-}C1}}$ lying 6.8 kcal mol^{-1} higher than $\mathbf{TS_{B1\text{-}C1}}$. C–N bond formation starting from **B1** was found to be an asynchronous process constituted by the following chemical

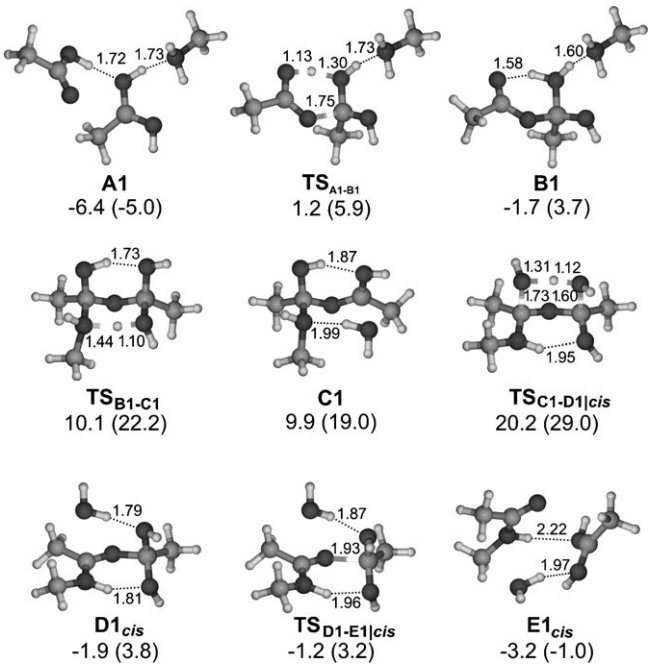
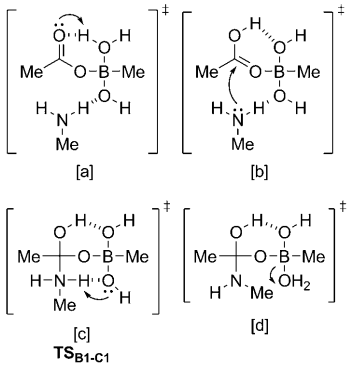


Figure 1. Optimized stationary points for the reaction of **1a** with **2a** catalyzed by boronic acid **4a**. Interatomic distances are expressed in Angstroms. MPW1K (B3LYP) solution energies are relative to isolated reactants and catalyst (**1a** + **2a** + **4a**) and are expressed in kcal mol^{-1}.

events: [a] proton transfer from a HO–B group to the carbonyl oxygen atom, [b] C–N bond formation, [c] proton transfer from the amino group to an oxygen atom, and [d] water dissociation from the boron center (Scheme 4). All the stationary points for this process could be located (see the Supporting Information) and the highest-energy first-order saddle point between **B1** and **C1** was found to be the transition state corresponding to N···H···O proton transfer [c].

Another crucial (and up to now neglected) aspect of the direct amide bond formation is the water-assisted dehydration step, which is required to generate the amide group after the nucleophilic addition. Formation of *cis*-**3a** was found to be favored, as $\mathbf{TS_{C1\text{-}D1|}_{cis}$ lies 5 kcal mol^{-1} lower than the corresponding transition state yielding the *trans* isomer. In view of



Scheme 4. Mechanism of C–N bond formation.

the relevance of steric repulsions for the stereoselectivity of amide bond formation, the transition states for water elimination have also been calculated using a computational model composed of compounds **1b**, **2b**, and **4b**. In total, fourteen isomeric transition states were optimized to account for the increased conformational complexity of this system ($\mathbf{TS}_{\mathbf{Ph1\text{-}7}|cis}$ and $\mathbf{TS}_{\mathbf{Ph1\text{-}7}|trans}$, see the Supporting Information). These calculations confirmed the trend observed with the smaller model (Figure 2).

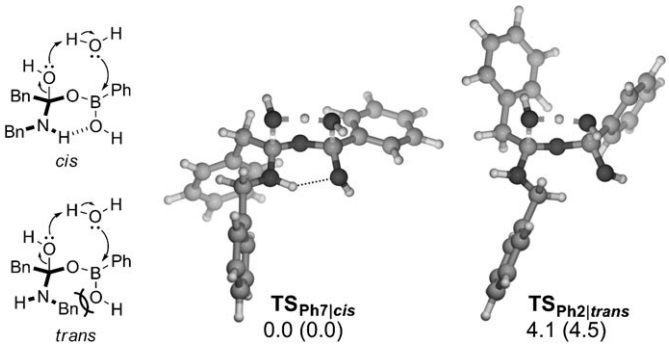


Figure 2. Lowest-energy water elimination transition states for the formation of *cis*-**3b** and *trans*-**3b** catalyzed by boronic acid **4b**. MPW1K (B3LYP) relative solution energies are in kcal mol^{-1}. Bn = benzyl.

In more detail, *cis* transition states benefit from an intramolecular N–H···O hydrogen bond. Also, the geometry required for *trans* amide formation suffers from steric interactions between the nitrogen substituent and the hydroxy group of the catalyst. This stereochemical prediction might have practical implications for challenging lactamization reactions, as the preferential formation of *cis* isomers would favor ring closure over oligomerization.[12]

The catalytic cycle ends with the dissociation of amide **3a** from boronic acid **4a** ($\mathbf{TS}_{\mathbf{D1\text{-}E1}|cis}$), which is predicted to be a facile process with a barrier of only 0.7 kcal mol^{-1}. Figure 3 summarizes the calculated potential energy profile for the most accessible reaction pathway. According to these data, formation of the boron-bound amide from the corresponding hemiaminal is the rate determining step of the reaction.

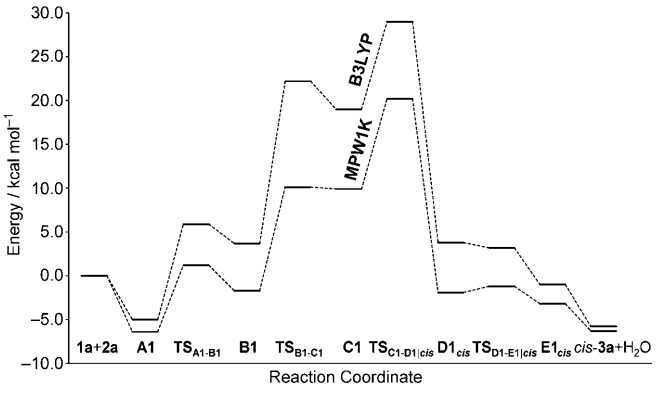


Figure 3. Calculated potential energy profile for the reaction of compounds **1a** and **2a** catalyzed by boronic acid **4a**.

Therefore, the overall solution barrier for the formation of amide **3a** catalyzed by boronic acid **4a** is the difference between the energy of hydrogen-bound complex **A1** and that of transition state $\mathbf{TS}_{\mathbf{D1\text{-}C1}|cis}$, which is calculated to be 26.6 kcal mol^{-1} by MPW1K and 34.0 kcal mol^{-1} by B3LYP.

These results were used to investigate the superior activity of *ortho*-halophenyl boronic acids (in the order I > Br > Cl > F).[8] Compound **4b** promotes the low-temperature formation of amide **3b**, although at a considerably decreased rate (31 % yield after 48 h at 40 °C, 10 mol % loading) compared to catalysts **4c** and **4d** (quantitative conversion after 48 h at RT, same loading). The experimental pK_a values of compounds **4b** and **4d** are virtually identical (8.8 and 8.9, respectively) and so are the calculated atomic charges on boron (+1.13 and +1.14). To test the different behavior of phenylboronic acids with and without a halogen atom as *ortho* substituent, the two stationary points employed to calculate the overall reaction barrier (corresponding to **A1** and $\mathbf{TS}_{\mathbf{C1\text{-}D1}|cis}$) were optimized for catalysts **4b**, **4c**, and **4d** using acid **1a** and amine **2a** as reactants.[13] The computational results are in excellent agreement with the experimental data, in that the overall barriers for the reaction catalyzed by **4c** and **4d** are respectively 0.9 and 1.7 kcal mol^{-1} lower than the value obtained with boronic acid **4b** (**4b**: 28.1 kcal mol^{-1}, **4c**: 27.2 kcal mol^{-1}, **4d**: 26.4 kcal mol^{-1}). For both catalysts **4c** and **4d**, the energetically most accessible transition states display a very short distance between the proton of the boron-bound oxydryl group and the halogen atom (Figure 4).[14] In other words, the calculations predict an O–H···X hydrogen bond as the reason for the improved activity of catalysts **4c** and **4d**.[15] The geometry of this interaction, featuring a C–X···H angle close to 90°, is in line with the well-known anisotropic electron distribution of carbon-bound halogens.[16] Visualization of the electrostatic molecular potential for $\mathbf{TS}_{\mathbf{iodo1}|cis}$ clearly displays a distortion of the iodine electron density in correspondence of the oxydryl proton (see Figure S3 in the Supporting Information). These results indicate that *ortho*-halophenylboronic acids act as bifunctional Lewis acid/Lewis base catalysts in this transformation.[17] At a first glance, this outcome could be rather surprising, as other catalysts containing better hydrogen-bond acceptors than halogens are not as efficient promoters of the amide bond formation. On the other hand, the intramolecular O–H···X hydrogen bond formed by *ortho*-halophenylboronic acids defines an additional six-membered ring in a transition state with several geometric constraints. It is therefore possible that the introduction of a halogen atom in the *ortho* position significantly increases the activity of catalyst

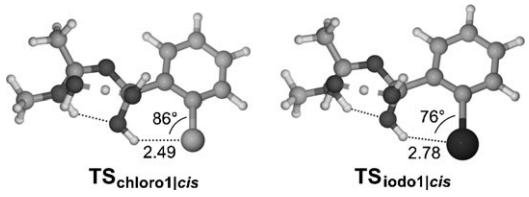


Figure 4. Lowest-energy water elimination transition states for the formation of *cis*-**3a** catalyzed by boronic acids **4c** and **4d**.

4b because of the ideal positioning of the Lewis basic site with respect to the boron-bound hydroxyl group.

In conclusion, the boronic acid catalyzed reaction between amines and carboxylic acids has been scrutinized theoretically using density functional calculations. The calculations predict hemiaminal dehydration to be rate-determining and indicate that, in this step, the formation of *cis* amides is significantly favored. The remarkable catalytic activity of *ortho*-halophenylboronic acids was rationalized in terms of the Lewis basicity of the halogens, that is, their capability to engage in an O–H···X hydrogen bond stabilizing the rate-determining transition state, which is greater for iodine than for chlorine.[15a] It is expected that these findings will aid the development of new catalytic systems with improved activity.

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