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Homologation of Boronic Esters with Organolithium Compounds: A Computational Assessment of Mechanism

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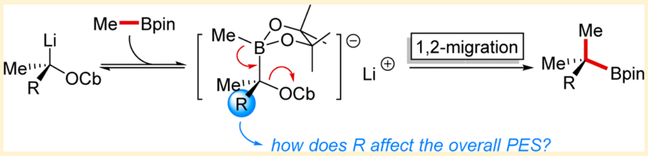
Supporting Information



ABSTRACT: Ab initio calculations are reported for the reaction of methyl boronic ester with organolithium reagents with α-leaving groups. The best calculations rely on density functional theory prediction of structures and coupled-cluster theory calculation of accurate potential energies. The results provide strong confirmation of the feasibility of a two-step mechanism with rapid initial formation of a boron−ate complex followed by slower migration of methyl from boron to carbon with loss of the leaving group. The calculated free energy of activation is consistent with observed kinetic behavior, and the calculations provide a framework for exploring substituent and other effects on reactivity. Obtaining reasonable agreement with experiment in this way is not trivial and requires careful treatment of level of theory (density functional theory calculations tend to yield inaccurate results), of conformational complexity, especially for the ate complexes, and of the nature of the microscopic model of reactants and solvent. The methodological challenges and possible pitfalls, many of which are relevant more broadly to computational modeling of organic reaction mechanisms, are discussed in detail.

INTRODUCTION

Boron compounds can be homologated by reaction with organolithium species containing a vicinal leaving group through a two-step mechanism involving initial formation of a tetracoordinate "ate" complex followed by 1,2-migration of one of the groups on boron and departure of the leaving group (Scheme 1).[1]

This reaction has been used in numerous syntheses in the group of one of us[2] as well as by many others.[3] In broad terms, the reaction mechanism of the overall transformation involves the two steps mentioned above. However, the design of efficient syntheses relying on the transformation requires an in-depth understanding of the mechanism including aspects such as the role of the migrating group, the other groups at boron, the leaving group, and the other reaction conditions such as solvent, temperature, and additives. To take one example, many applications of this homologation reaction have used Hoppe's lithiated carbamates as the carbenoid reagent,[4] but for some migrating groups this leads to low reactivity in the migration step and to erosion of yield and selectivity. Using better leaving groups such as α-lithiated hindered benzoates leads to improved results,[5] suggesting that the migration step is rate-limiting. On the other hand, the erosion of selectivity suggests that formation of the ate complex is reversible under certain conditions.[6] Understanding such effects and being able to use them when designing syntheses requires a fundamental insight into the effect of leaving groups and migrating groups on the mechanism.

Computational methods are well suited to exploring reaction mechanisms, providing a detailed atomistic picture of the structures of key intermediates and transition states that can thereafter be used as a basis for designing new reactions. For example, we used computational methods some time ago to explore the mechanism of epoxide formation from aldehydes and sulfur ylides.[7] This study focused on the mechanism of a generic, nonchiral version of the reaction, seeking to understand the origin of diastereoselectivity. However, the resulting mechanistic model could then be applied to understand the observed diastereo- and enantioselectivity when using a broad range of sulfur ylides obtained from chiral sulfides.[8] Our aim in the present project was to develop a similar mechanistic framework for the homologation reaction of boronic esters.

Atomistic modeling of the reactivity of organolithium species has long been recognized as especially challenging for reasons that are essentially connected to the highly ionic nature of the C−Li bond.[9] This has a number of consequences that make computational studies more difficult than is the case for reactions of less polar species. A first factor is the tendency of organolithium compounds to form aggregates such as dimers or tetramers which exist in equilibrium with monomeric R−Li species.[10,11] While this has been recognized since the early days of computational organolithium chemistry,[10] it places severe demands on the size of the atomistic model used in calculations to explore reactivity, and these demands are by no means easy to accommodate. A second factor is that the lithium center tends to interact strongly with neighboring groups and solvent so as to complete its first ligand sphere, so that counterions or

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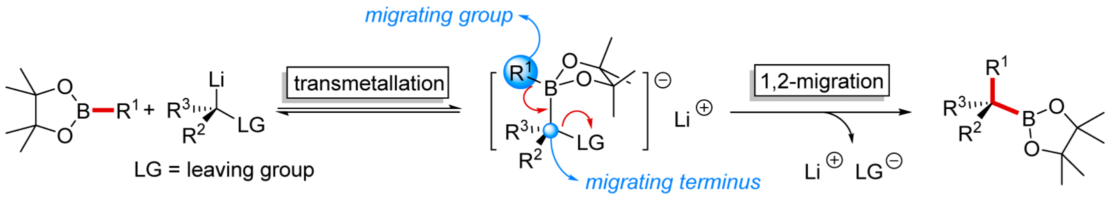
Scheme 1. Homologation of Boronic Esters by Lithiation−Borylation



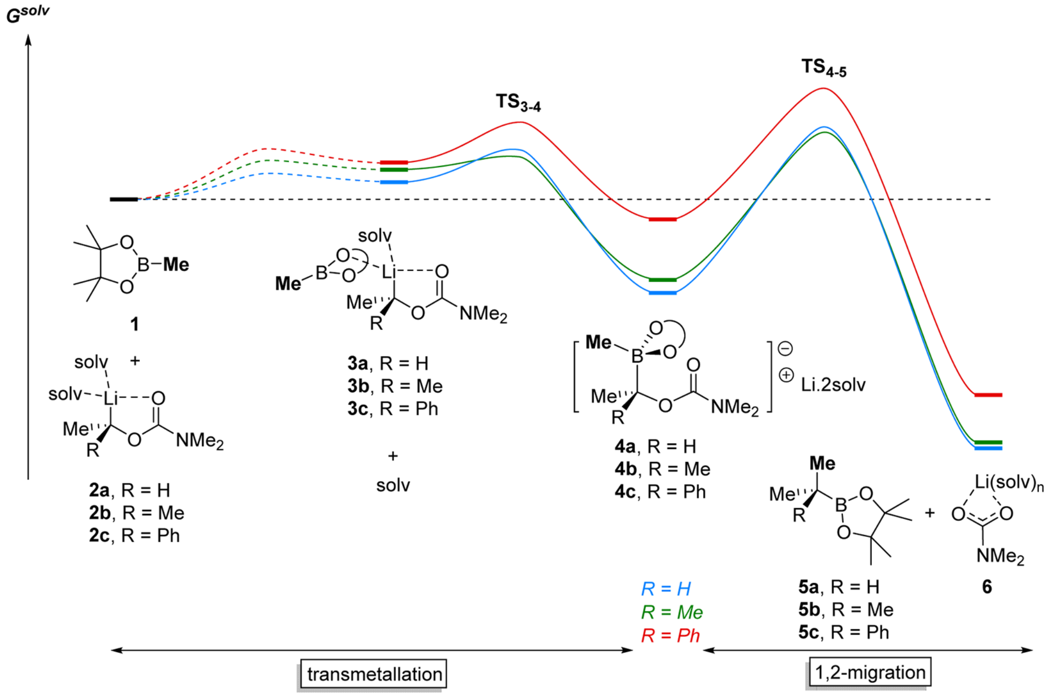


Figure 1. Schematic free energy surface for the lithiation−borylation reaction.

solvent molecules need to be included in the microscopic model used in computations in order to get reasonable results.[12] Also, organolithium chemistry involves polar and indeed ionic species so that treatment of bulk solvation effects is essential in order to obtain accurate energies. Finally, reactions tend to be carried out in relatively nonpolar environments, so that ionic species are typically not fully dissociated as they would be in aqueous solution but exist instead in tight ion aggregates with ill-defined structures. All of these features place significant demands on computation. While modern studies in computational organolithium chemistry are able to cope with these demands,[13−15] the field remains much more challenging than is the study of many other organic reactions.[11]

In this study, we use advanced electronic structure methods to derive a microscopically correct model for the reaction of homologation of lithiated carbamates with boronic esters. We have found that as well as paying careful attention to aspects such as solvation, it is necessary to use careful screening of conformational space and very high-level electronic structure theory to obtain results that agree with the observed kinetic behavior of this system. Accordingly, as well as presenting our best results concerning what we believe to be the correct mechanism, we will also describe some of the modeling pitfalls encountered during the work. Some of these are specific to the boron−lithium chemistry involved in the target reaction, while others are generic to organolithium and indeed organic chemistry.

COMPUTATIONAL METHODS

Calculations were performed using a composite approach aimed at yielding the highest possible accuracy for relative free energies. Geometry optimizations and frequency calculations were performed at the B3LYP-D2/6-31+G(d) level of theory[16,17] using the GAUSSIAN 09 suite of programs.[18] Tight convergence criteria as well as ultrafine integration grids were used in order to ensure satisfactory convergence. This is necessary because some of the species under study, in particular the ate complexes, present a number of low frequency vibrational modes (<100 cm^{-1}) that contribute significantly to the entropy. The smallest frequencies involved in the present study are of the order of 10−15 cm^{-1}. Anharmonic or other more sophisticated treatment of vibrational entropy might therefore lead to changes in calculated free energy of the order of 1 kcal mol^{-1}. Solvent effects were modeled by explicitly incorporating solvent molecules into the model, which is commonly referred to as microsolvation. In order to minimize computational costs, the experimental solvent (diethyl ether) was represented by the slightly smaller dimethyl ether. This reduces the number of atoms in the microsolvated species and more importantly leads to models with a much simpler conformational space. Though this approximate treatment of the microsolvating solvent has been used frequently in the literature and is generally accepted to be reliable, its validity in our case has been carefully considered and will be discussed later. Bulk solvent effects (Et_2O) were computed as a single point using a corrective continuum model (SMD)[19] on the gas-phase-optimized structures at the same level of theory. The stationary points were characterized by full calculation of vibrational frequencies. Gibbs energies at 298.15 K were computed on the basis of the rigid rotor/harmonic oscillator approach to statistical mechanics. Gibbs energies as output by Gaussian, which refer to an ideal gas ($p = 1$ atm) standard state, were corrected to use a standard state corresponding to species in solution with a standard concentration of 1 M (solute species) or 9.55 M (diethyl ether solvent, considered here to be the pure liquid, which is appropriate for a fairly dilute reaction mixture)

$$G^\circ = G^{1\text{atm}} + RT\,\ln(C^\circ/C^{1\text{atm}})$$

where G° is the Gibbs energy with reference to the correct solution-phase standard state, $G^{1\text{atm}}$ is the ideal gas standard Gibbs energy at 298.15 K assuming a 1 atm standard state (as output by Gaussian), C° is the standard reference state concentration (1 or 9.55 M), and $C^{1\text{atm}}$ is the concentration of an ideal gas under the standard $p = 1$ atm conditions ($C^{1\text{atm}} = 1/V_m = P/RT = 0.0409$ mol l^{-1} for an ideal gas at 298.15 K and 1 atm). Numerically, the corrective term in the above equation is equal to 3.2 kcal mol^{-1} per diethyl ether molecule and 1.9 kcal mol^{-1} per any other molecule at 298.15 K. Solvation equilibria are particularly sensitive to this correction:

$$\underset{+1.9}{\text{R–Li·2solv}} \rightleftharpoons \underset{+1.9}{\text{R–Li.solv}} + \underset{+3.2}{\text{solv}}$$

Finally, electronic energies were recomputed at a higher level of theory. A first set of electronic energies ($E^{\text{gas},1}$) was obtained by doing single-point calculations using the bigger 6-311+G(d) basis set and replacing the D2 dispersion correction by the newest D3 correction[20] (BJ damping[21]); a second set of electronic energies ($E^{\text{gas},2}$) was obtained by doing single-point correlated ab initio calculations using a highly accurate composite method based on coupled-cluster theory (see the Supporting Information for full details). The latter calculations were performed using the Molpro 2010.1 package.[22]

Finally, free energies in solution were estimated as

$$G^{\text{solv},x} = G^\circ + (E^{\text{solv},0} - E^{\text{gas},0}) + (E^{\text{gas},x} - E^{\text{gas},0})$$

where $x = 0$ refers to B3LYP-D2/6-31G(d), $x = 1$ refers to B3LYP-D3/6-311+G(d), and $x = 2$ refers to LCCSD(T0)-F12/VDZ-F12.

RESULTS AND DISCUSSION

Mechanistic Study. The reaction outlined in Scheme 1 is very general, and experiments have involved very many different variants on this basic scheme. It is well beyond the scope of this work to attempt to model the mechanism of all of them or, indeed, of a representative set of reaction conditions. Accordingly, we have made some choices and assumptions to limit the scope of the work, and we start by outlining these and justifying them.

In our calculations, we have addressed three related reactions (Figure 1). In each case, the boronic ester **1** is one of the reactants, and the leaving group in the organolithium compound **2** is a dimethylamino carbamate group. Three different substitution patterns are considered for **2**, with one methyl group present in each case, whereas the other vicinal position is occupied respectively by H, Me, and Ph substituents in **2a**, **2b**, and **2c**. These three target reactions are typical of the systems studied experimentally.[23] The chemistry is typically carried out in ether solvents. In order to describe solvation, we used a mixed explicit and implicit model. Some of the solvent molecules coordinate strongly to lithium, and these ligands occupying the first coordination sphere are treated explicitly here, as dimethyl ether. The bulk solvent is described using a continuum model of diethyl ether.

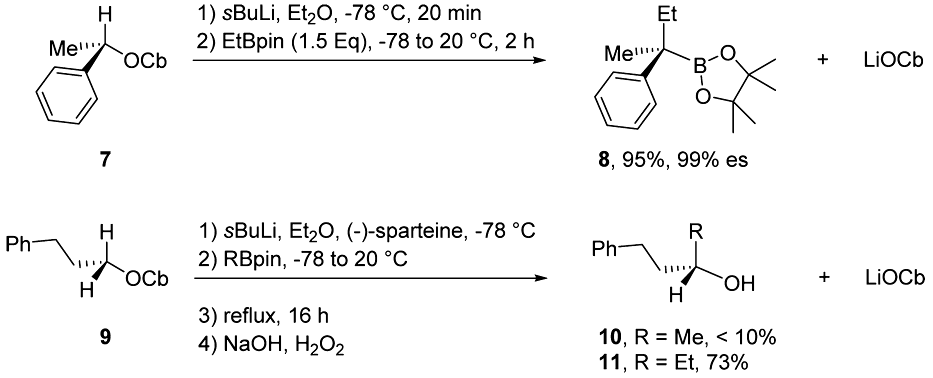
The organolithium compound **2** is modeled as a disolvated species. Together with the alkyl group and the chelating carbamate carbonyl oxygen, this brings the coordination number of the lithium center to four. Test calculations exploring the preferred solvation state of some organolithium species are discussed below. We note that in some cases the organolithium species similar to **2** are generated in the presence of an additional ligand, typically a chelating diamine such as TMEDA or sparteine. In such cases, these strong ligands are expected to remain coordinated to lithium throughout the subsequent steps in the reaction, and this may affect the overall energetic profile. However, the reaction is also often carried out under diamine-free conditions, and the model used here is aimed at describing this type of reaction.

Many organolithium compounds exist as aggregates, typically dimers and tetramers, in equilibrium with monomers. In our calculations, we have assumed that all species exist as monomers. Given the presence of the carbamate group and its preference for chelation to lithium, it is likely that **2** would not form very stable tetramers. However, dimer species could, in principle, be formed. Previous work[14] suggests that with bulky secondary or tertiary alkyllithium species, as here, the equilibrium is less shifted toward aggregates. We note that experiments do not highlight any strong effects of concentration nor do they provide evidence of formation of very stable dimers, so we assume that if dimers can be formed, they are in reasonably favorable equilibrium with the monomers modeled here.

The first step in the reaction is formally a ligand exchange at lithium, with an oxygen atom of the boronic ester replacing one of the solvent molecules. Solvent exchange at lithium is very fast in simple systems such as lithium salts in water,[24] with a rate constant of the order of 10^9 s^{-1} at room temperature. Considering that the incoming water molecules have a concentration of 55 M, this is equivalent to a second-order rate constant of ca. 10^7 M^{-1} s^{-1} or a free energy of activation of ca. 8 kcal mol^{-1}. Solvent-exchange rate constants in more complex species such as the dimer of lithium hexamethylsilazide have been measured for a number of solvents,[25] and correspond to free energies of activation between 7 and 11 kcal mol^{-1}. We have not explored this step computationally due to the conformational challenge associated with locating the corresponding transition states. Instead, we simply assume that the barriers will be under 10 kcal mol^{-1}, as for these related processes. The exchange process is unfavorable in terms of the equilibrium free energy by a few kcal mol^{-1}. This is partly due to the different standard state used for the diethyl ether solvent (pure liquid) and the incoming **1** (1 M solution), reflecting the fact that displacing solvent is unfavorable. However, the magnitude of the change is larger than would be expected from concentration terms only, also presumably reflecting the slightly less donating character of the oxygen lone pairs of the boronic ester.

The second step shown in Figure 1 is transmetalation. Transition states leading from **3** to the ate complexes **4** have been located, which have the character of a very loosely structured σ-metathesis process, with the C–B bond forming in concert with C–Li bond breaking. This whole process—boronic ester ligation to the metal followed by metathesis through a four-membered ring transition state is in some ways analogous to the process involved in reaction of boronic acids with Pd(II) complexes as part of Suzuki–Miyaura coupling,[26] though in that case the carbon nucleophile migrates from boron to palladium, whereas here it instead migrates from lithium to boron. There are presumably many different pathways that lead to **4** from **3**, and we have only located the TSs that lead directly from low energy conformers of **3**. As this step is not crucial in

Scheme 2. Experimental Conditions for Selected Lithiation−Borylation Reactions



determining the overall reactivity as a function of the nature of the migrating and leaving groups, we have not made an exhaustive search for all possible TSs. It should be noted that in chiral versions of the reaction, the transmetalation plays an important role in determining the chirality of the product. Transmetalation TSs that proceed with retention at carbon lead to overall net inversion (since the migration step occurs with inversion), whereas TSs that proceed with inversion lead to overall retention. The TSs located here are of the first type, and this is more or less required when starting from the intermediate **3**, as the coordination of the boronic ester to the lithium naturally places the boron atom in a position in which it must attack the carbon center from the "front side".

Formation of **4** from **3** is calculated to be very favorable in free energy, and indeed, the ate complex **4** is predicted to be much more stable than reactants. Formation of the ate complex is found to be less favorable in the case of **4c**, i.e., when R = Ph, which is not unexpected since in this case the lithiated carbamate **2c** is stabilized by the phenyl group. As discussed below, this conclusion is rather dependent on the level of theory used. Also, some discussion of the structure of **4** is warranted. In Figure 1, **4** is shown as an ion pair, with a dissociated lithium ion. This is not completely correct in that the preferred conformation of this species involves definite bonding between the lithium ion and the ate species, with the carbamate carbonyl and the boronic ester both remaining coordinated to lithium, and the change in structure with respect to **3** is much smaller than suggested in the representation of Figure 1.

The final step in the mechanism is the migration of the methyl group from boron to carbon, together with the departure of the carbamate group. This step, or similar ones with a different migrating group, a different leaving group or different substituents at boron, has been studied in a significant number of previous computational studies.[27−29] The TS structures obtained are rather similar to those found in previous studies, with the migrating group positioned somewhere between the boron and carbon atoms, and a clear S_N2-like trigonal bipyramidal arrangement of groups around the latter. The barrier is also found to be substantial, and is predicted to be rate-limiting for product formation at room temperature for all three reactions studied here. However, except in the case of reaction of **4c**, it is close in free energy to the TS for transmetalation and indeed to the barrier to ligand exchange at lithium leading from reactants to **3**.

Link to Experiment. We now discuss how these calculated free energy surfaces relate to experiment. This is somewhat difficult as many variants of the target reactions have been studied experimentally, and the models studied here do not correspond *exactly* to any of these variants. However, very similar cases have been studied and this allows us to confront our results with observed kinetic behavior. The closest links to experiment are for the reaction of the lithiated carbamates **2a** and **2c** for which Scheme 2 shows related reactions together with the conditions used and the observed outcome.[1b,5]

For the benzylic system **7**, mixing of the lithiated carbamate and the boronic ester is observed by NMR to lead rapidly to ate complex formation at the low temperature used for initial mixing. This is consistent with the low barriers discussed here for ligand exchange and for transmetalation. The ate complex then undergoes migration leading to product. This is observed to be slow at −78 °C since the ate complex is relatively stable at that temperature but occurs reasonably rapidly as the reaction mixture is warmed. Our calculated free energy of activation for this step for the model system **4c** is of 26.8 kcal mol^{-1} (see Table 1). This value is computed for a temperature of 298.15 K, but is not expected to vary substantially as this is a unimolecular rearrangement step, with a potential energy barrier (27.1 kcal mol^{-1} at the same level of theory) which is close to the free energy barrier. For a barrier of 26.8 kcal mol^{-1}, reaction is predicted to be exceedingly slow at −78 °C, whereas at room temperature, it would lead to a rate constant of ca. 0.0004 h^{-1} according to the Eyring equation. This is somewhat smaller than the implied rate constant given that reaction is observed to occur in ca. 2 h at room temperature,[1c] which suggests a rate constant of the order of 1 h^{-1} or a free energy barrier of the order of 22 kcal mol^{-1}. This error could be due to errors in the computational method such as the use of B3LYP-D2 for geometry optimization, the combination of LMP2-F12 and

Table 1. Gibbs Free Energies in Solution (Et_2O) Computed at the LCCSD(T0)-F12/VDZ-F12//B3LYP-D2/6-31+G(d) Level of Theory (See Text and Supporting Information for Details)[a]

	R = H	R = Me	R = Ph
1 + 2	0.0	0.0	0.0
3 + solv	3.7	5.7	6.5
$\mathbf{TS}_{3-4}$	8.8[b]	8.0	13.2
4	−17.9	−15.3	−6.8
$\mathbf{TS}_{4-5}$	12.7 [30.6]	12.4 [27.7]	20.0 [26.8]
5 + 6	−60.6	−59.7	−51.7

[a] Energies given in kcal mol^{-1}. Activation barriers given in brackets. [b] Geometry optimization performed without dispersion.

LCCSD(T0), or the treatment of entropy. However, the implied error of ca. 5 kcal mol^{-1} in our results seems too large to be due only to such factors, based on previous work in our group.[30] Instead, it seems likely that the problem lies with the choice of our computational model, which does not correspond exactly to the actual system, in a number of ways. Experimentally, the leaving group is a diisopropylamino carbamate, whereas we have used dimethylamino carbamate. The solvent used experimentally is diethyl ether. We use a continuum model of this solvent but model the explicit solvent molecules as dimethyl ether. Finally, the experiment involves migration of an ethyl group originating from EtBpin, whereas we model a methyl group. Methyl is known to be a poor migrating group compared to primary and secondary alkyl groups and has in fact often been referred to as a nonmigrating group in the context of rearrangement of nonsymmetrical organoborate complexes.[31] Some of these choices could of course be modified, but given that our aim was to obtain a general understanding of the homologation reactions, and the considerable computational expense of repeating the calculations, we consider that the agreement obtained here is acceptable.

The second example given in Scheme 2 relates to the model lithiated carbamate **2a**. Experimentally, the 1,2-metalate rearrangement requires higher temperatures (35 °C) as well as longer reaction times than benzylic systems, suggesting a higher activation barrier for this step. Our computational results are in line with this observation, with a free energy of activation of 30.6 kcal mol^{-1} for the model system **4a** compared to 26.8 kcal mol^{-1} for **4c**. This second example also illustrates well the poor migratory aptitude of methyl mentioned above, with a yield going from less than 10% for methyl migration to 73% for ethyl migration, all things being equal. The poor reactivity of methyl substituted boronic esters is accompanied by a slight erosion of selectivity. This is what one would expect according to our results, since the TS for 1,2-migration lies above the TS for transmetalation.

The calculations show that the free energy of the migration TS lies *above* the free energy of reactants and of the TSs leading to formation of **4c** from reactants. This means that ate complexes such as **4c** should be in equilibrium with reactants, although the latter should be in very low concentration and may not be observable. This agrees well with the experimental observation that formation of the ate complex is reversible for hindered boronic esters and racemization of the lithiated carbamate sometimes competes with migration.[2d,6]

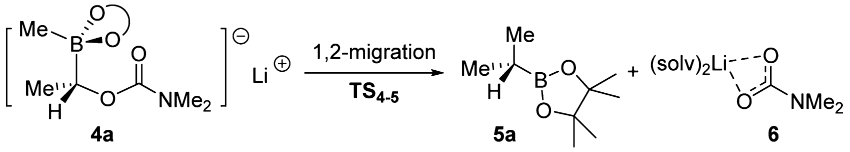
Methodological Pitfalls. As mentioned in the introduction, computational study of reactions of organolithium compounds is challenging. This is certainly what we have found during this study, and we now wish to discuss some of the methodological issues that arose in the present study. These relate to the level of theory, the treatment of solvation, and the conformational complexity. Many of the issues encountered here arise in other computational studies of organolithium chemistry and indeed in computational mechanistic studies in general. We believe that a lack of attention to these aspects can lead to results that are "consistent with experiment" but are in reality not "right for the right reason". To obtain robust mechanistic conclusions, a more careful approach is needed in which each of the above difficulties is dealt with carefully and hereby explain this in more detail.

Level of Theory. We start by discussing the role of the level of theory, based on the relative potential energies calculated in vacuo using various methods, as shown in Table 2. We have carried out geometry optimization of all species using density functional theory, as this represents a good combination of accuracy and efficiency in many cases. The B3LYP functional was chosen due to convenience and familiarity with the properties of this very widely used functional. However, there has been very extensive evidence in recent years that relative energies computed with B3LYP are not accurate whenever one considers processes in which large numbers of atoms either come into or cease to be in van der Waals contact with one another.[32] This problem, which is due to very poor treatment of dispersion interactions in B3LYP and many other common DFT functionals, is expected to be relevant for a number of processes in the present study, especially for solvent coordination to the organolithium species and for ate complex formation. Accordingly, we have used a version of B3LYP semiempirically corrected to take into account dispersion, namely the B3LYP-D2 functional.[17] This provides the base case for our study. When comparing calculated results to experiment, it became obvious that this method does not provide a robust description of reactivity in these systems, and we have accordingly supplemented the B3LYP-D2 geometry optimizations with extensive single-point calculations using other methods.

First of all, we consider the energies computed using B3LYP itself, i.e., without any dispersion correction. As can be seen in Table 2, this method predicts a much higher energy relative to reactants for both the ate complex **4a** and the migration TS compared to the dispersion corrected case. This is what would be expected given the fact that **4a** is generated from two separate molecules being brought together. As can be seen, the difference in relative energies from B3LYP-D2 to B3LYP is substantial, of approximately 20 kcal mol^{-1} (entry 1 vs 2). This too is in line with what has been observed in many previous examples.

Given the presence of partial negative charges and formally negatively charged species, we also assessed the role of diffuse functions on relative energies, reoptimizing the structures using the 6-31+G(d) basis set (entry 3). When doing so, we found that it was also necessary to use tight optimization convergence criteria and ultrafine DFT integration grids in order to obtain robustly converged structures. As can be seen in Table 2, diffuse functions do increase the relative energy of **4a** and the TS, presumably due to a decrease in basis set superposition error, but the effect is not major. Likewise, using single-point energy calculations with the larger 6-311+G(d) basis (entry 4) does not seriously affect energies. Using the more recent D3 version of the dispersion correction makes a bigger change. As is often observed this tends to lead to slightly smaller relative energy changes compared to B3LYP compared to those obtained with B3LYP-D2 (entry 5).[33] Finally, we include the results from the two ab initio methods used here: MP2 (entry 6) and CCSD(T) (entry 7). Due to the large size of the system, we do not use the standard canonical implementations of these methods, which would be prohibitively expensive (at least when using reasonably large basis sets), but the local implementations. We also use an explicitly correlated variant of MP2 (F12) to reach energies that are close to the infinite basis set limit. As can be seen, these methods suggest that the ate complex **4a** is slightly less stable than predicted by B3LYP-D3 and that the TS is significantly higher in energy. This mirrors an observation made in an earlier study of a related boron−ate complex migration reaction,[28] where TS energies were found to be much

Table 2. Effect of the Level of Theory on the Overall Energy Profile[a]



entry	geometry optimization [convergence, integration grid]	electronic energy single-point	E^{gas} (kcal mol^{-1})	
			4a	**TS_{4-5}**
1	B3LYP-D2/6-31G(d) [default, default]	B3LYP/6-31G(d)	−23.3	2.8 [26.1]
2	B3LYP-D2/6-31G(d) [default, default]	B3LYP-D2/6-31G(d)	−44.9	−17.0 [27.9]
3	B3LYP-D2/6-31+G(d) [tight, ultrafine]	B3LYP-D2/6-31+G(d)	−41.8	−15.2 [26.6]
4	B3LYP-D2/6-31+G(d) [tight, ultrafine]	B3LYP-D2/6-311+G(d)	−42.0	−16.3 [25.7]
5	B3LYP-D2/6-31+G(d) [tight, ultrafine]	B3LYP-D3/6-311+G(d)	−38.8	−14.8 [24.0]
6	B3LYP-D2/6-31+G(d) [tight, ultrafine]	LMP2-F12/VDZ-F12	−37.4	−7.3 [30.1]
7	B3LYP-D2/6-31+G(d) [tight, ultrafine]	LCCSD(T0)-F12/VDZ-F12	−35.5	−3.7 [31.8]

[a] Energies given with respect to the separated reactants MeBpin + MeCHLiOCb·$2Me_2O$. Activation barriers given in brackets.

higher with MP2 than with B3LYP. This is presumably due to an incorrect treatment of nonstatic correlation by the DFT functional in the strongly delocalized SN2-like TS.[34]

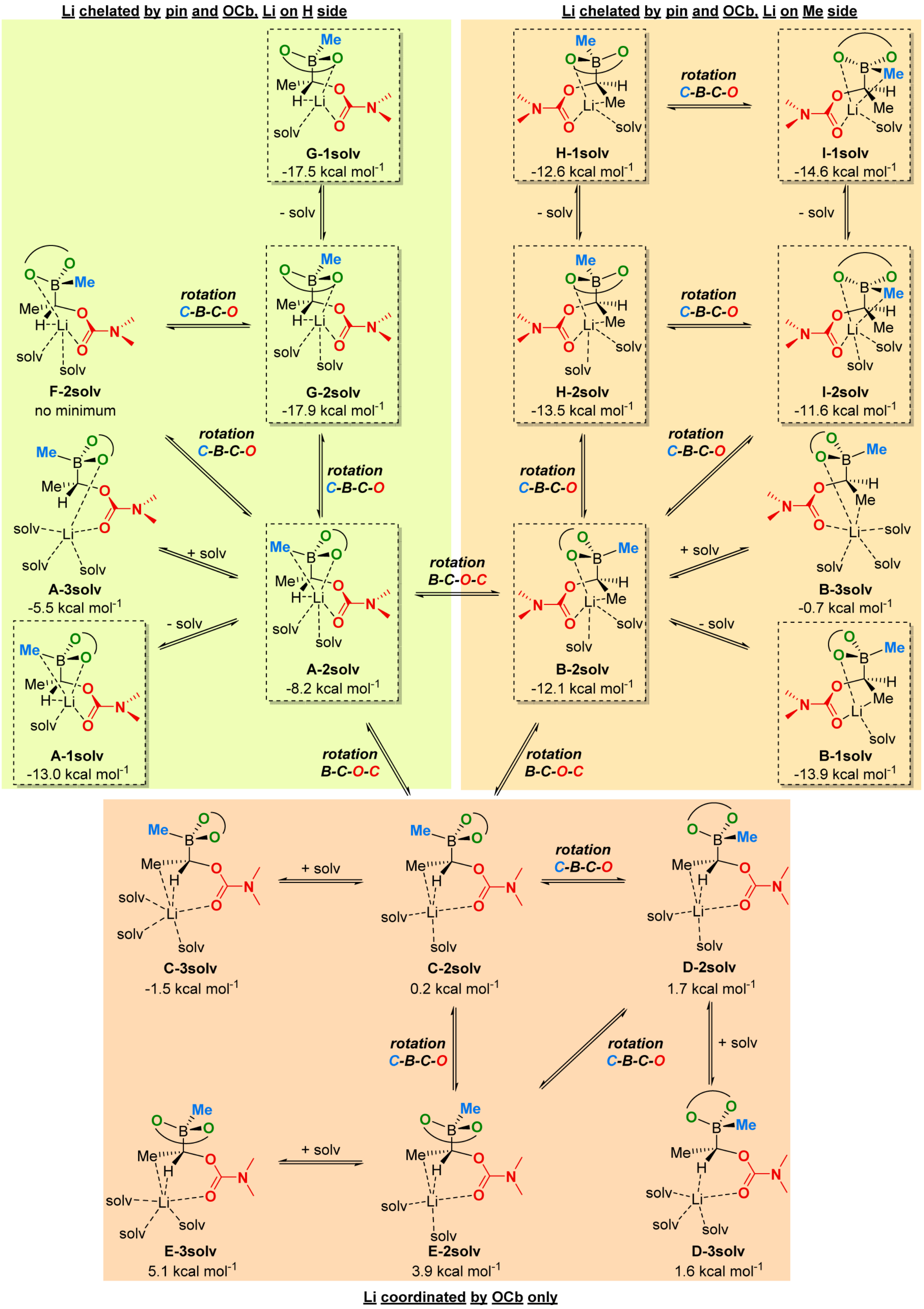
It is interesting to compare the potential energy in Table 2, entry 7, with the free energy in Table 1. The loss of entropy associated with ate complex formation is substantial and means that the two sets of values are very different. In the past, mechanistic studies tended to rely on potential energies rather than free energies to assess reactivity, perhaps with some qualitative consideration of entropy. The present comparison indicates why this is bound to be difficult. It is also instructive to see that the potential energies with B3LYP (Table 2, entry 1) are fairly similar to the free energies of Table 1. The entropic effect destabilizes the ate complex and TS, whereas dispersion stabilizes it. This rough cancellation of error may explain in part why it has been argued that entropy terms in solution should be scaled or omitted[35] as this, together with inaccurate B3LYP energies, leads to acceptable agreement with experiment. This seems plausible given that it is known that molecules experience a significant change in entropy upon passing from the gas phase to solution.[36] When using more accurate electronic structure calculations, good agreement with experiment is obtained[30] when the full gas-phase entropy (adapted to the correct standard state, as in this work) is used. This suggests that any major changes in entropy upon solvation are treated at least approximately by the continuum solvent model, and we assume here that the approach outlined in the Computational Methods is adequate to reach accuracy of ca. 1 kcal mol^{-1}. More sophisticated approaches taking into account excluded volume effects[37] might, however, be helpful especially for obtaining refined estimates for the free energy of pure liquids and concentrated solutions.

Conformational Analysis. We now turn to consider the role of conformational freedom. All species involved in this study can potentially exist in multiple conformers, but this is a particularly significant problem when considering the ate complexes **4**, which can be thought of as displaying the properties of very tightly bound ion pairs. This means that as well as the internal degrees of freedom of the borate complex, associated with rotation around the B−C and other single bonds, one must also consider a variety of different positions for the lithium ion, as well as a different number of solvent molecules coordinated to this ion and their own internal degrees of freedom. This makes it difficult to compute the relative free energy of **4** compared to reactants. One possible approach to deal with this issue is to treat **4** as a free anion, with a completely separate solvated lithium ion, but given the tight nature of binding of the two ions, this would lead to significant errors in free energy. Hence, we sought to map out the conformational space available to **4** in detail and to assess the implications for mechanistic studies. This has been done most thoroughly for **4a**, and the results are presented here. We have also explored how the relative energy of different conformations of **4a** depends on level of theory, and surveyed the conformations of **4b** and **4c**. These results are discussed in the Supporting Information.

We have considered a large number of conformations of the ate complex **4a**, with differences in the number of solvent molecules coordinated to lithium as well as in the relative orientation of different groups (Scheme 3). Initially, we considered structures with either two or three solvent molecules. We anticipated that disolvated complexes would feature lithium in a tetrahedral environment and therefore lie lower in free energy than the corresponding trisolvated complexes. However, gas-phase geometry optimization led to higher coordination numbers for lithium (5 or 6) due to additional coordination by either the substituents on the migrating terminus or the migrating group itself, or both. For this reason, the "best" conformers were reoptimized with one solvent molecule only, and the results are discussed at the end of this section. The initial conformation considered, **A**, corresponds to the structure in which the methyl group on boron is *anti* to the leaving group and the lithium atom sits between the carbamate, one oxygen of the pinacol, the methyl group on boron, and the hydrogen on the migrating terminus. Lithium is hexacoordinated in the disolvated structure **A-2solv** ($Li\cdots O_{pinacol}$ = 2.025 Å; $Li\cdots H_{terminus}$ = 2.101 Å; $Li\cdots O_{carbamate}$ = 1.922 Å; $Li\cdots H_{migrating}$ = 2.115 Å; and $Li\cdots O_{solvent}$ = 1.992/2.095 Å). Addition of an extra solvent molecule leads to the pentacoordinated structure **A-3solv**, in which both lithium−hydrogen interactions have disappeared ($Li\cdots O_{pinacol}$ = 1.912 Å; $Li\cdots O_{carbamate}$ = 2.119 Å; and $Li\cdots O_{solvent}$ = 2.070/2.147/2.213 Å). Both of these structures are exergonic with respect to the separated reactants (ΔG^{solv} = −8.2 kcal mol^{-1} and −5.5 kcal mol^{-1} respectively).

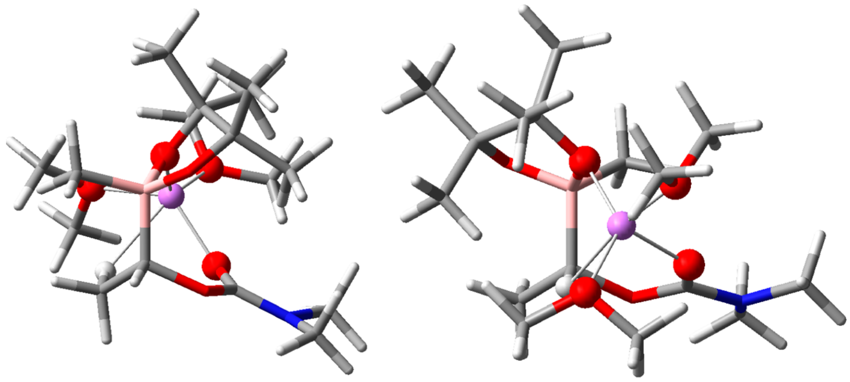
Conformations **B** and **C** can be thought of as being generated by rotation around the $C_{terminus}$−O bond in **A**. In the disolvated structure **B-2solv**, lithium sits between the

Scheme 3. Conformational Analysis of the Ate Complex 4a[a]



[a] Free energies in solution (Et_2O) computed at the LCCSD(T0)-F12/VDZ-F12//B3LYP-D2/6-31+G(d) level of theory (see text and Supporting Information for details) and given with respect to the separated reactants MeBpin + MeCHLiOCb·$2Me_2O$.

carbamate, the second oxygen of the pinacol and the methyl group on the migrating terminus (Li···$O_{pinacol}$ = 1.832 Å; Li···H = 2.337 Å; Li···$O_{carbamate}$ = 1.881 Å; and Li···$O_{solvent}$ = 1.993/2.065 Å). The methyl group coordinates lithium by one of its



B-2solv **G-2solv**

Figure 2. Optimized geometries of B-2solv and G-2solv: gray, carbon; white, hydrogen; purple, lithium; red, oxygen; blue, nitrogen.

hydrogens, in an η^1 fashion. Surprisingly, this conformation lies lower in free energy than **A-2solv** even though the lithium atom seems to be located in a more crowded position (ΔG^{solv} = −12.1 kcal mol^{-1}). Contrary to what happens with **A**, addition of an extra solvent molecule does not break the methyl-lithium interaction but instead leads to a structure in which lithium is hexacoordinated (Li···$\mathrm{O_{pinacol}}$ = 1.953 Å; Li···H = 2.060 Å; Li···$\mathrm{O_{carbamate}}$ = 1.950 Å; and Li···$\mathrm{O_{solvent}}$ = 2.105/2.152/2.313 Å). This conformation lies more than 10 kcal mol^{-1} above the corresponding disolvated one. The last of these three conformers, **C**, corresponds to the lithium ion sitting opposite to boron, between the carbamate and the two substituents (Me and H) on the migrating terminus. The loss of the pinacol-lithium interaction strongly disfavors this conformation, and both the disolvated and trisolvated structures are found to lie much higher than **B** in free energy (ΔG^{solv} = 0.2 kcal mol^{-1} and −1.5 kcal mol^{-1}, respectively).

Conformations **D** and **E** can be formed by rotation around the $\mathrm{C_{terminus}}$−B bond starting from **C**. Just as for **C**, these structures do not allow interaction between the lithium ion and the pinacol oxygens and are, as a consequence, high in free energy. Indeed, irrespective of whether disolvated or trisolvated variants are considered, all conformations in these families lie higher in free energy than the separated reactants. It is noteworthy that addition of a third solvent molecule in this case is not as unfavorable as found previously, owing to the fact that lithium is more electron-deficient in **C**, **D**, and **E** than it is in **A** and **B**.

Starting from **A**, two new conformers, namely **F** and **G**, were constructed by rotation around the $\mathrm{C_{terminus}}$−B bond. Despite many attempts, no local minimum corresponding to **F** could be localized. The disolvated complex **G-2solv**, on the other hand, was found to lie very low in free energy (ΔG^{sol} = −17.9 kcal mol^{-1}), i.e. almost 10 kcal mol^{-1} below **A-2solv**. In this structure, lithium is pentacoordinated, interacting with the pinacol, the carbamate and the hydrogen on the migrating terminus (Li···$\mathrm{O_{pinacol}}$ = 1.817 Å; Li···$\mathrm{H_{terminus}}$ = 2.125 Å; Li···$\mathrm{O_{carbamate}}$ = 1.894 Å; and Li···$\mathrm{O_{solvent}}$ = 1.991/2.047 Å). Half of the difference in free energy between **A-2solv** and **G-2solv** arises from differences in entropic contributions, showing that relative potential energies do not always provide the full picture. Two new conformers **H** and **I** were derived from **B** by rotation around the $\mathrm{C_{terminus}}$−B bond. Lithium is pentacoordinated in both structures, interacting with the methyl on the migrating terminus in **H-2solv** and the methyl on boron in **I-2solv**. The two conformers are found to lie close to **B-2solv** in free energy (ΔG^{solv} = −13.5 kcal mol^{-1} and −11.6 kcal mol^{-1} respectively).

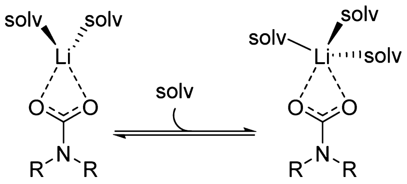
Finally, conformers **A**, **B**, **G**, **H**, and **I** were reoptimized with only one solvent molecule. All monosolvated complexes are found to lie very close in free energy to the corresponding disolvated ones, suggesting an equilibrium between the two solvation states. However, because lithium is disolvated in the initial lithiated carbamate **2**, we have decided to consider only disolvated complexes in our mechanistic analysis in order to limit errors in the estimation of entropic contributions.

In conclusion, we have localized eight conformers of **4a** in different solvation states, with free energies ranging between −17.9 and 5.1 kcal mol^{-1} relative to the separated reactants. We have found a strong preference for chelation of lithium by one oxygen on the pinacol and the carbonyl oxygen. Numbers given in Tables 1 and 2 refer to the "best" conformer **G**. It should be noted that this conformer does not lead to *C*-migration but instead is a precursor for the competing *O*-migration reaction, which has been observed experimentally.[2d,27c] This goes beyond the scope of this study and has not been considered further. The "best" conformer in which the migrating group is *anti* to the leaving group is **B** and lies 6 kcal mol^{-1} above **G**. The *C*-migration step therefore involves an equilibrium between **G** and **B**, followed by 1,2-migration and departure of the leaving group. Optimized geometries of **B-2solv** and **G-2solv** are depicted in Figure 2.

The range of computed energies for the different conformers is very broad. We have found that this is true also for $\mathbf{TS_{4-5}}$, with the results shown earlier in the paper only including the values obtained for the most favored conformer. A full analysis of the conformational landscape in this reaction would require that we examine the transition states involved in interconversion of the conformers, but this very demanding task went beyond the scope of this work and we have instead assumed that the free energy barriers involved are lower than the barriers to chemical reaction from one species to another. Perhaps the key message is that it was not at all straightforward to predict in advance of the calculations which conformer would be favored. Also, the gaps in free energies between different conformers are substantial. This is a problem for any computational study of reactions of this type, as the conclusions in terms of reactivity may be significantly affected by how fully the conformational landscape has been covered.

Solvation of Lithium. A final issue we have considered here concerns the choice of computational model. Since the early days of mechanistic organolithium computational studies,[10] computers have become much faster and more efficient methods have been developed. This makes it much less necessary to consider heavily truncated models. However, for reactions in solution, some form of truncation of the atomistic model is still needed, and the practicalities of considering all possibly relevant conformers of a system may still mean that it is desirable to truncate even the chemically reacting system. This is what was done in the present study: the diisopropyl carbamate leaving group was replaced by a dimethyl carbamate group and the explicit Et_2O solvent molecules were replaced by Me_2O molecules. These simplifications drastically reduce the number of atoms and the number of conformations for each ate complex and transition state. In order to get a feeling of how these simplifications affect the overall energetic profiles, we performed a series of tests on a simple equilibrium. Enthalpies of solvation for R_2NCO_2Li calculated at the B3LYP or B3LYP-D2 level of theory are summarized in Table 3. Entry 3 represents our best estimate (R= *i*-Pr and solv = Et_2O). We considered Me_2O and THF as potential models for Et_2O. Although THF has broadly the same number of atoms as Et_2O, it reduces computational costs by limiting the conformational space associated with each complex. All things being equal, Me_2O and THF appear to bind more strongly to lithium than Et_2O (respectively entry 4 vs 3 and entry 2 vs 3) by about 5 kcal mol^{-1}, in agreement with the higher Lewis basicity of Me_2O and THF.[38] Despite this, we have decided to model the explicit solvent molecules by Me_2O but note that this is a potential source of error wherever species with a different number of solvent molecules coordinated to lithium are considered. On the other hand, implicit solvation by either THF or Et_2O leads to the same results (entry 1 vs 2). Replacement of *i*-Pr substituents by Me groups appears to have a negligible impact on the solvation enthalpy (entry 4 vs 5), comforting us in our choice to use a truncated carbamate in our calculations.

Table 3. Choice of the Computational Model. All Calculations Performed at the B3LYP-D2/6-31+G(d) Level of Theory



entry	explicit solvent	R	implicit solvent (SMD)	$H^{solv,0}$ (kcal mol^{-1})
1	THF	*i*-Pr	THF	−10.4
2	THF	*i*-Pr	Et_2O	−10.5
3	Et_2O	*i*-Pr	Et_2O	−6.7
4	Me_2O	*i*-Pr	Et_2O	−10.0
5	Me_2O	Me	Et_2O	−10.4

CONCLUSION

In conclusion, we have carried out an extensive set of calculations in order to develop a consistent atomistic model of the reaction of α-lithiated carbamates with boronic esters. The calculations show that a pathway involving net front-side substitution of the lithium atom by boron to form an ate complex, followed by 1,2 migration, is a convincing candidate for the overall reaction mechanism. In this mechanism, the formation of the ate complex from separated reactants is predicted to be reversible under some conditions, especially with more stabilized organolithium compounds. The barrier to migration is predicted to be large, and to determine reactivity. The barrier is large enough to account for the observed slow reaction in some variations on this transformation. While similar conclusions have been reached in some previous studies, the present high level of theory and careful treatment of conformational effects provides new and strong evidence to support them. The detailed model developed here can now be used to explore variations and understand aspects such as the effect of the migrating group, the effect of the structure of the organolithium species, and so on.

The reaction studied here is one of many where the results obtained can depend quite strongly on the computational approach used. As a result, it is perfectly possible to imagine that a relatively low quality calculation can fortuitously appear to be highly consistent with one or more of the experimental observations. To avoid this outcome, it is necessary to pay attention to a number of important aspects. In a second part of the paper, we therefore discuss some of the pitfalls that can be encountered in this type of mechanistic study of organolithium chemistry, and what we have done to avoid them. One perennial problem in computational studies of reactivity is being able to carry out calculations of sufficient accuracy. This applies here, too, with, for example, use of a standard DFT functional without dispersion correction clearly leading to very inaccurate energies. Even dispersion-corrected B3LYP does not yield accurate results due to an incorrect description of electron correlation in the migratory substitution TS. Another problem here is conformational complexity. This is a particular problem in organolithium chemistry due to the large number of species with lithium−solvent interactions and anion−cation ion-pairing. We have shown that a key intermediate displays very extensive conformational complexity. Any computational study that does not identify the correct conformers for a given intermediate or TS may obtain very inaccurate energetics irrespective of the electronic structure method used−or may yield "good" results in a poorly fortuitous way. Finally, we point out that choosing the computational model for organolithium chemistry is not always straightforward. We recommend that computational studies of reaction mechanisms in large organic systems routinely discuss (perhaps in the Supporting Information of a paper) aspects such as efforts made to assess all relevant conformers and sensitivity of results to level of theory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional details, absolute energies, enthalpies, and free energies computed at the B3LYP-D2/6-31+G(d) level of theory, three lower frequencies, and Cartesian coordinates of all optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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