Complex-Induced Proximity Effects in Directed Lithiations: Analysis of Intra- and Intermolecular Kinetic Isotope Effects in Directed Aryl and Benzylic Lithiations

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Abstract: The mechanism of proton transfers in directed lithiations has been investigated by measuring the intra- and intermolecular kinetic isotope effects for the benzylic lithiation of *N*-benzyl-*N*,*N*′-dimethyl urea (**6**) and the ortho lithiations of the tertiary amide *N*,*N*-diisopropylbenzamide **(7**) and the secondary amide *N*-isopropylbenzamide **(8**) by *sec*-BuLi/TMEDA in THF. For the lithiation of **6**, a large primary kinetic isotope effect is observed for intramolecular competition of monodeuterated substrate, and a much smaller apparent isotope effect is seen for the intermolecular competition between diprotiated and dideuterated substrates. These results support a two-step mechanism of largely irreversible initial complexation between the substrate and the organolithium reagent, which is followed by hydrogen transfer to the organolithium reagent for the directed lithiation of urea **6**. Indistinguishable limits for large intermolecular and intramolecular isotope effects are measured for the lithiations of **7** and **8**. The directed lithiations of amides **7** and **8** are suggested to proceed by a two-step mechanism in which initial complexation is largely reversible.

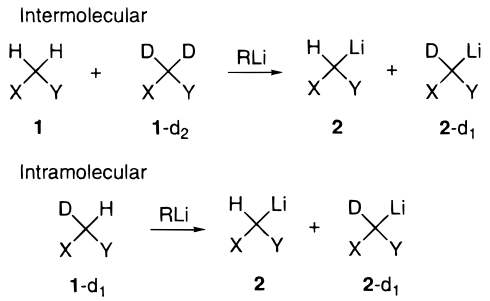
Introduction

Directed deprotonative lithiation of organic substrates by organolithium bases, followed by treatment of the intermediate organolithium substrate with an electrophile, is a widely used synthetic approach for the regio- and stereoselective creation of new carbon−carbon and carbon−heteroatom bonds.[1] The mechanism of directed lithiations continues to be the subject of theoretical and experimental investigations. An early hypothesis, advanced to account for regioselective lithiation of aromatic compounds bearing a Lewis basic heteroatom, is that the lithium coordinates with the lone pairs of the heteroatom of the directing group to form a pre-lithiation complex.[2] This complex brings the lithiating agent in close proximity to the acidic hydrogen, thereby accounting for the observed regioselectivity. Complex-induced proximity effects (CIPEs) have been used to rationalize many apparently anomalous observations in organolithium chemistry.[1a] There is abundant evidence for coordination of lithium to heteroatoms in ground states,[3] but the evidence that pre-lithiation complexes are, in fact, on the reaction pathway is more limited.[4]

An alternative hypothesis is that a directing group kinetically accelerates the transfer of a nearby hydrogen to the base by binding in the transition state for the deprotonation. In this model, there is not an intermediate with a finite lifetime on the reaction pathway prior to proton transfer. Any stable coordinated species which might be formed are involved in non-productive equilibria. The term "kinetically enhanced metalation" has been suggested as an apt description of this proposal.[5]

The determination of intramolecular and intermolecular isotope effects can provide evidence for the presence of intermediates along the reaction pathway after the rate-determining step of the reaction. Reactions in which two symmetrical protons are available for removal can be investigated by this method. The intramolecular experiment involves replacing one of two prospective hydrogens with deuterium and measuring the selectivity of proton vs deuteron removal. The intermolecular competition experiment measures the relative rates of proton and deuteron transfers in unlabeled and dideuterated substrates.[6]

In the lithiation of **1**, an intermolecular isotope effect would be measured for the reaction of **1** and **1**-d_2 by the ratio of conversions of **1** to **2** and **1**-d_2 to **2**-d_1 upon reaction with a deficient amount of organolithium base. An intramolecular isotope effect is measured by the ratio of **2** to **2**-d_1 from the lithiation of **1**-d_1.



Possible reaction pathways for the conversion of **1** to **2** either directly or via the intermediate **3** are illustrated by the qualitative

(1) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(2) Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658.

(3) Jones, F. N.; Zinn, M. F.; Hauser, C. R. *J. Org. Chem.* **1963**, *28*, 663. Streitwieser, A., Jr. *J. Organomet. Chem.* **1978**, 156. Jastrzebski, J. T. B. H.; Voten, G. v.; Konikn, M.; Stam, C. H. *J. Am. Chem. Soc.* **1982**, *104*, 5490. Setzer, W.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24* 353. Streitwieser, A., Jr.; Williams, J. E.; Alexandralos, S.; McKelveg, J. M. *J. Am. Chem. Soc.* **1987**, *98*, 4778. Slsher, V.; Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. *Chem. Rev.* **1991**, *91*, 137. Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlberch, H. *Chem. Ber.* **1993**, *126*, 1887. Reich, H. J.; Gudmundsson, B. O. *J. Am. Chem. Soc.* **1996**, *118*, 6074. Saá, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, *61*, 5194. Hay, D. R.; Gallagher, D. J.; Du, H.; Long, S. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 11391.

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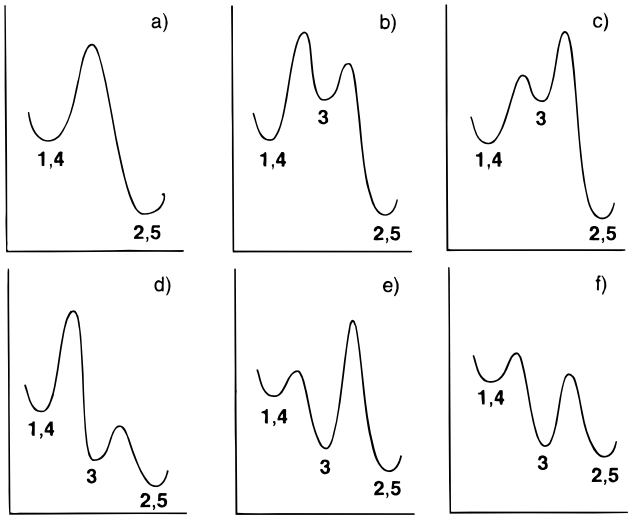
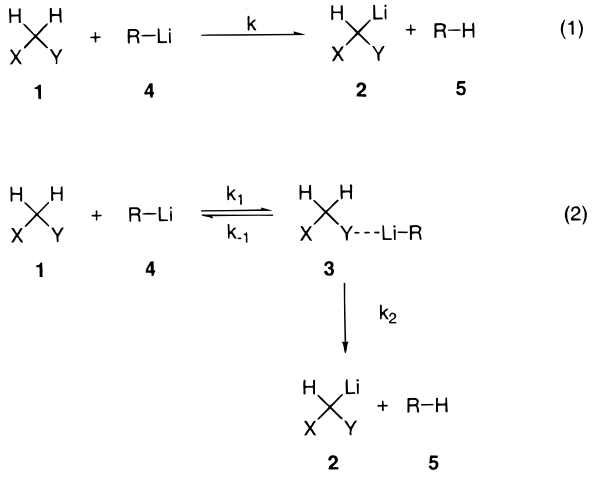


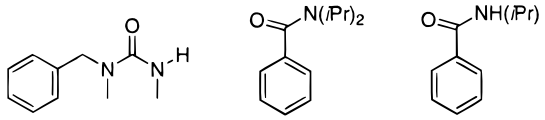
Figure 1. Qualitative energy diagrams for one- and two-step mechanisms.

energy diagrams in Figure 1. The kinetically enhanced metalation would be a one-step mechanism via a single transition state arising from simultaneous complexation and proton transfer, as shown in Figure 1a. Reaction via a complex would be a two-step mechanism, and the possibilities are shown in Figure 1b−f. The formation of an intermediate which is higher in energy than the reactants may possess a rate-limiting first step (Figure 1b) or a second step (Figure 1c). The formation of an intermediate which is lower in energy than the reactants can proceed through a slow first step (Figure 1d), a fast, reversible first step (Figure 1e), and a fast, but irreversible first step (Figure 1f).



Depending on the profile of the reaction, measurements of the intra- and intermolecular isotope effects may or may not give the same apparent isotope effect. If the reaction proceeds through a single step (Figure 1a), the ratio **2** to **2**-d_1 would be determined solely by the primary isotope effect in both the intramolecular and intermolecular experiments. Hence, the same value for k_H/k_D would be obtained in each case, ignoring any small secondary isotope effects. Similarly, if the starting materials **1** and **4** and a complex **3** can interconvert (Figure 1c,e), the observed isotope effect for each experiment would be determined by the primary isotope effect on the proton/deuteron removal step. Again, the same value for k_H/k_D would be measured in both experiments. However, if the reaction proceeds through either a slow or irreversible (Figure 1b,d,f) first step, then different isotope effects would be measured in the two experiments. The k_H/k_D value measured by the intramolecular isotope effect experiment would be determined by the primary hydrogen/deuterium isotope effect, but the value for the intermolecular isotope effect would be determined by the kinetic isotope effect on the first step of the mechanism. If this step is assumed to be complexation, then that isotope effect is expected to be very small.

A range of primary hydrogen−deuterium isotope effects have been observed for a number of directed lithiations.[4e,7] We have used intermolecular and intramolecular isotope effects to study the directed lithiation of urea **6**.[4e] More recently, Stratakis has employed this approach in the study of the ortho lithiation of anisole.[8] Very small intermolecular and intramolecular isotope effects ($k_H/k_D = 2-3$) were reported in the presence and absence of TMEDA. Collum's group has measured the rates of proton and deuteron transfers independently and found a much higher value for an intermolecular comparison ($k_H/k_D = 20$).[9] In this report, we determine the intra- and intermolecular isotope effects for a benzylic and two ortho lithiations by investigation of the reactions of urea **6**, tertiary amide **7**, and secondary amide **8** with *sec*-BuLi/TMEDA in THF at −78 °C.



6 **7** **8**

Results

Previously we communicated that, when **6** is treated with *sec*-BuLi/TMEDA at −78 °C and reacted with an electrophile, the α-substituted product is obtained in high yield. In addition, the intermolecular and intramolecular isotope effects were determined using dimethyl sulfate as an electrophile.[4e] We have reinvestigated this system using anhydrous CO_2 as the electrophile to eliminate any possible isotopic contamination from proton sources in the electrophile. The results are summarized below for the reaction of **6**-d_1 and **6**-d_0/**6**-d_2 with *sec*-BuLi/TMEDA.

Treatment of **6**-d_1 (1.4% d_2, 94.9% d_1, 3.7% d_0)[10] with 1.8 equiv of *sec*-BuLi/TMEDA for 15 min at −78 °C in THF, followed by reaction with an excess of anhydrous CO_2, provided

(4) (a) Meyers, A. I.; Funetes, L. M.; Reiker, W. F. *J. Am. Chem. Soc.* **1983**, *105*, 2082. (b) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263. (c) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145. (d) Warmus, J. S.; Rodkin, M. A.; Barkley, R.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1993**, 1357. (e) Resek, J. E.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 405. (f) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092. (g) Luitjes, F. J. J. de Kanter; Schakel, M.; Schmitz, R. F.; Klumpp, G. W. *J. Am. Chem. Soc.* **1995**, *117*, 4179.

(5) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755. van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Tetrahedron* **1994**, *50*, 5903. Kremer, T.; Junge, M.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 3345.

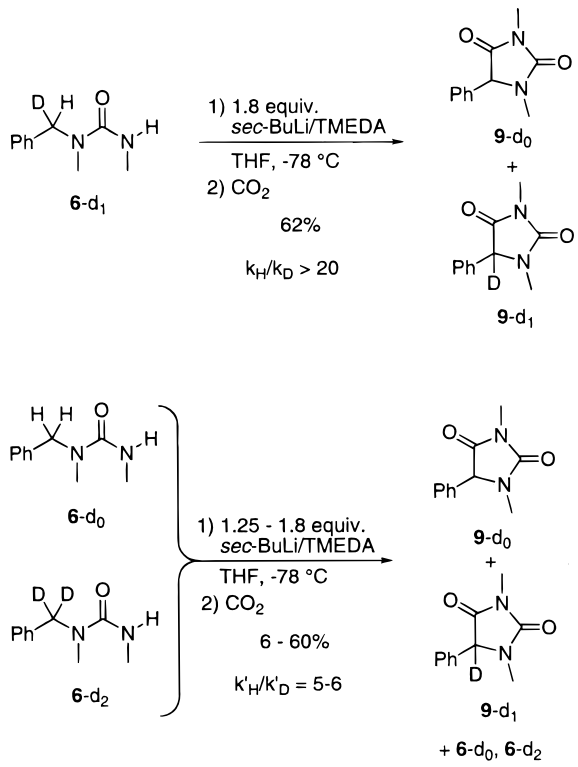
(6) Determination of intermolecular and intramolecular isotope effects is a powerful tool for the evaluation of mechanistic alternatives. See: Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126 and references therein.

(7) (a) Hoppe, D.; Paetow, M.; Hinter, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394. (b) Clayden, J.; Pink. J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1998**, *39*, 8377.

(8) Stratakis, M. *J. Org. Chem.* **1997**, *62*, 3024.

(9) Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421.

(10) All isotope ratios were determined by FI/MS of materials judged to be of >95% purity by spectroscopic and chromatographic techniques. The error for this method is taken to be ±5%. Errors in mass determination are assumed to be ±0.1 mg, and all errors are propagated through calculations by standard techniques.



product **9** (94% d_1, 6% d_0) in 62% yield after separation from unreacted **6** (3.5% d_2, 94% d_1, 2.9% d_0). The isotope effect for the intramolecular competition experiment is given simply by the isotopic ratio of the product shown in eq 3, corrected for the presence of d_0 material.[11] This product ratio will be independent of the extent of reaction.

$$\left(\frac{k_H}{k_D}\right)_{intra} = \left(\frac{[\mathbf{9}\text{-}d_1]}{[\mathbf{9}\text{-}d_0]}\right) \tag{3}$$

The isotopic enrichment of the product is consistent with a large isotope effect, ($k_H/k_D = 45 \pm 26$).[12] The large error in this measurement is due to the low occurrence of d_0 material in the product relative to the uncertainty of the measurement, as discussed in detail in the Supporting Information. In this work, we find that high isotope effects are difficult to determine precisely, and we prefer to conclude that the intramolecular isotope effect for the reaction of **6**-d_1 is >20.

Treatment of a mixture of **6**-d_0 and **6**-d_2 with a deficient amount of lithiating agent (1.25−1.8 equiv of *sec*-BuLi/TMEDA) at −78 °C, followed by reaction with CO_2, provided **9** in 6−60% yield. The product was separated from unreacted **6**, and the isotopic abundances of each were determined. Calculation of the intermolecular isotope effect from the isotopic ratios of the starting materials and products is more complicated, as the relative concentrations of **6**-d_0 and **6**-d_2, and therefore the relative forward velocities of reaction, change as a function of time. To account for this, the reaction is assumed to be first order in substrate, and the relative rates of proton and deuteron transfers for **6**-d_0 and **6**-d_2 are given by eq 4, where [**6**-d_0]° and [**6**-d_2]° are the initial concentrations of **6**-d_0 and **6**-d_2, respectively, and [**6**-d_0]/[**6**-d_0]° and [**6**-d_2]/[**6**-d_2]° are the fractions of **6**-d_0 and **6**-d_2 remaining, respectively.

$$\left(\frac{k'_H}{k'_D}\right)_{inter} = \left(\frac{\log([\mathbf{6}\text{-}d_0]/[\mathbf{6}\text{-}d_0]^\circ)}{\log([\mathbf{6}\text{-}d_2]/[\mathbf{6}\text{-}d_2]^\circ)}\right) \tag{4}$$

The extent of reaction can be determined from either the reactant or the product, that is,

$$\left(\frac{[\mathbf{6}\text{-}d_0]}{[\mathbf{6}\text{-}d_0]^\circ}\right) = \left(\frac{([\mathbf{6}\text{-}d_0]^\circ - [\mathbf{9}\text{-}d_0])}{[\mathbf{6}\text{-}d_0]^\circ}\right) \tag{5}$$

and similarly for **6**-d_2,

$$\left(\frac{[\mathbf{6}\text{-}d_2]}{[\mathbf{6}\text{-}d_2]^\circ}\right) = \left(\frac{([\mathbf{6}\text{-}d_2]^\circ - [\mathbf{9}\text{-}d_1])}{[\mathbf{6}\text{-}d_2]^\circ}\right) \tag{6}$$

Equations 5 and 6 are valid only with quantitative recovery of all materials. When material balances are lower, the two methods of calculating the extent of reaction were averaged, and the uncertainty was taken to be half of the range.

For example, when a mixture of **6**-d_0 and **6**-d_2 (60% d_2, 38% d_0)[13] was treated with 1.8 equiv of *sec*-BuLi/TMEDA in THF at −78 °C for 15 min, followed by reaction with CO_2, **9** (45% d_1, 55% d_0) was isolated in 62% yield, and 28% of unreacted **6** (95% d_2, 3.5% d_0) was recovered. The apparent isotope effect $(k'_H/k'_D)_{inter} = 6 \pm 1$, and a measurable amount of the original **6**-d_0 was recovered unreacted. The error reflects the uncertainty not only in the isotopic abundance in the starting material and products, but in the percent conversion as well. Repetitive experiments were carried out to 49% and 54% yields and gave apparent isotope effects of 6 ± 2 and 7 ± 2, respectively. At very low conversions (ca. 6%) for the reaction of **6**-d_0 and **6**-d_2, the apparent isotope effect was found to be 3 ± 3. The large error associated with this value is a result of the large uncertainty in the measurements of the extent of reaction due to low material balances. A value for k'_H/k'_D of 5−6 is assigned for the reaction of **6**-d_0 and **6**-d_2.[14]

We have also investigated the intermolecular and intramolecular isotope effects for the ortho lithiations of **7** and **8**. In our experiments with **7**, little of the deuterium is removed from **7**-d_1, rendering the precise measurement of **10**-d_0, and therefore the ratio (**10**-d_0/**10**-d_1), difficult. Accordingly, these isotope effects are most appropriately discussed in terms of their lower limits. Treatment of **7**-d_1 (99.5% d_1, 0.5% d_0) with a slight excess of *sec*-BuLi/TMEDA in THF, followed by reaction with CO_2, gave **10** (97.2% d_1, 2.8% d_0)[15] in 73% yield. This corresponds to an isotope effect of 34 ± 4. However, repetitive experiments gave isotope effects of 65 ± 7 and 49 ± 10. We attribute the large range of these data to the difficulty of accurately defining the amount of **10**-d_0 in the presence of large amounts of **10**-d_1. While quantitative evaluation of the intramolecular isotope effect is not possible from these data, the isotope effect is clearly very large, and we assign it a value of >30. An intramolecular isotope effect for **7**-d_1 has recently been reported by Clayden and co-workers to be >50 for the reaction of **7**-d_1 with *sec*-BuLi, followed by treatment with methyl iodide.[7b]

(11) The difference between the amount of d_0 starting material recovered and the original amount of d_0 starting material was assumed to be found as **9**-d_0. Sample calculations are presented in the Supporting Information.

(12) The error was determined by propagation of the error of the individual measurements. The errors in determining the relative amounts of products and the extent of reaction are the principle contributors to the large uncertainties in the isotope effects. For a detailed discussion of the error assessment, refer to the Supporting Information.

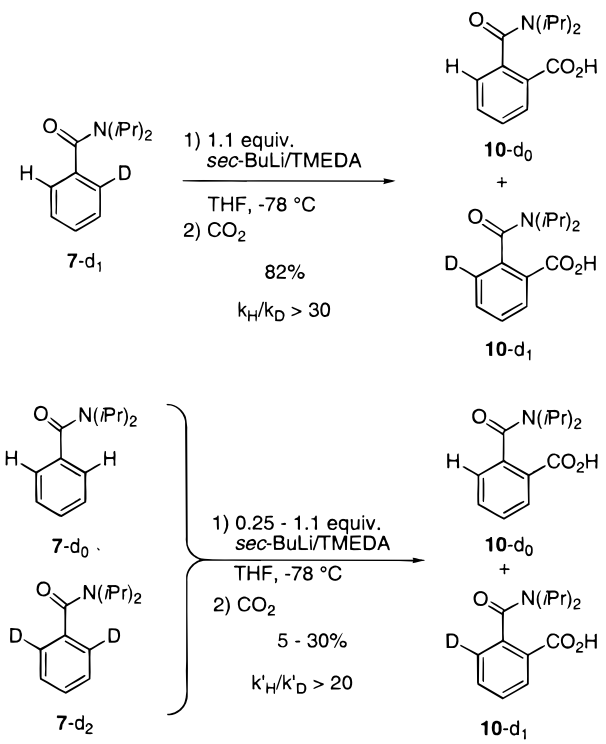
(13) The starting materials need not be in a 1:1 ratio, since only the extents of reaction of each species are compared.

(14) Beginning with the N−D analogues of **6**-d_1, **6**-d_0, and **6**-d_2 or **8**-d_1, **8**-d_0, and **8**-d_2 had no effect on the measured k_H/k_D or k'_H/k'_D values.

(15) Acids **10** and **11** were converted to *N*-isopropylphthalimide (**12**) for analysis by mass spectrometry.[25]

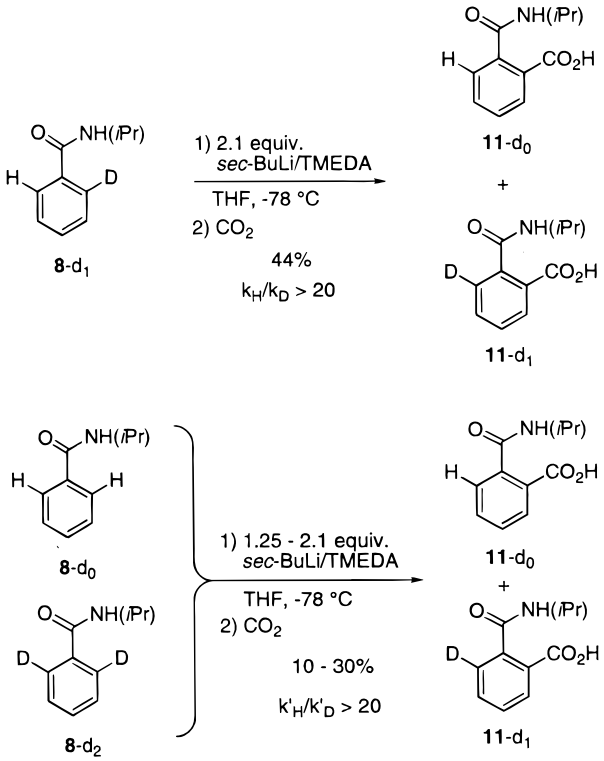
The intermolecular isotope effect for **7** was determined to be large, albeit in experiments which illustrate the limits of these measurements. When mixtures of **7**-d_0 and **7**-d_2 were treated with deficient amounts of *sec*-BuLi/TMEDA, essentially all of the d_0 material reacted before a detectable amount of the d_2 material was found to react. For example, when a mixture of **7**-d_0 and **7**-d_2 (50% d_0, 50% d_2) was treated with 0.25 equiv of *sec*-BuLi/TMEDA and then reacted with CO_2, **10** (99% d_0, 1% d_1) was isolated in 14% yield, and 73% of **7** (41% d_0, 59% d_2) was recovered unreacted. The isotope effect cannot be calculated from the above data, as a measurable amount of **7**-d_2 did not react, and therefore determination of the extent of reaction of **7**-d_2 is impossible. Similarly, treatment of a mixture of **7**-d_0 and **7**-d_2 (57% d_0, 43% d_2) with 0.45 equiv of *sec*-BuLi/TMEDA and reaction with CO_2 gave **10** (99% d_0, 1% d_1) in 39% yield, and 46% of unreacted **7** (23% d_0, 76% d_2) was recovered. Again, the isotope effect cannot be calculated directly from these data because a measurable amount of **7**-d_2 did not react. However, it is noteworthy that 75% of the initial **7**-d_0 was converted to product, consistent with a very large isotope effect.

Reaction of a mixture of **7**-d_0 and **7**-d_2 (46% d_0, 54% d_2) with 0.7 equiv of *sec*-BuLi/TMEDA, followed by treatment with CO_2, afforded **10** (62% d_0, 38% d_1) in 68% yield, and 14% of unreacted **7** (23% d_0, 76% d_2) was recovered. In this case, the extent of reaction of **7**-d_2 can be measured, but essentially no **7**-d_0 remains in the starting material, and therefore the relative rates of **7**-d_2 and **7**-d_0 were not measured, and an isotope effect cannot be calculated. Attempts to collect data where the extents of conversion of **7**-d_0 and **7**-d_2 were directly comparable were unsuccessful. A lower limit on the isotope effect can be assigned by noting that at least 75% of **7**-d_0 reacted before 5% of the **7**-d_2 reacted. This would correspond to an intermolecular isotope effect of at least 20.



The ortho lithiation of secondary amide **8** was examined and found to give an intramolecular isotope ratio that was also very high. Starting from **8**-d_1 (97% d_1, 3% d_0), **11** (95.3% d_1, 4.7% d_0) was obtained in 44% yield, and 45% of **8** (97.6% d_1, 1.5% d_0) was recovered. This would correspond to an isotope effect of 20 ± 3 before correcting for reaction of residual **8**-d_0 in the starting material. Precise determination of the isotope effect is complicated by the low occurrence of **11**-d_0, coupled with uncertainty regarding the exact amount of **11**-d_0 due to reaction of the residual **8**-d_0. Nevertheless, the intramolecular isotope effect can be assigned to be >20.

Measurements of the intermolecular isotope effect were complicated by the low conversions of **8**-d_2 material in concert with high conversions of **8**-d_0; within the limits of detection, no reaction of **8**-d_2 was observed prior to complete consumption of **8**-d_0. For example, when a mixture of **8**-d_0 and **8**-d_2 (30% d_0, 70% d_2) is treated with 1.5 equiv of *sec*-BuLi/TMEDA and reacted with CO_2, **11** (5% d_0, 95% d_1) is isolated in 27% yield, and 58% of **8** (3% d_0, 97% d_2) is recovered unreacted. The calculated value for the extent of reaction of **8**-d_2 is not above the uncertainty of the measurement, while more than 90% of the **8**-d_0 has reacted. These observations are consistent with a large isotope effect, which we assign a value of >20.[14]



Discussion

The experimental results can be discussed in terms of the qualitative energy diagrams shown in Figure 1. If there is no complex along the reaction pathway, (Figure 1a) and the rate acceleration and regioselectivity of the reaction are only due to stabilization of the transition state for the proton-transfer step, each experiment would measure the same apparent isotope effect, assuming a negligible secondary isotope effect.[16] Alternatively, if there exists a preequilibrium complex between the substrate and the organolithium base, followed by slow deprotonation (Figure 1c,e), the intra- and intermolecular experiments will also yield the same isotope effect. However, if a step prior to deprotonation is of substantially higher energy than proton transfer, there will be no intermolecular isotope effect revealed by the product ratio, assuming that the rate of complexation is unaffected by the labeling (vide supra).

(16) Lowery, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper Collins: New York, 1987; pp 238−240.

The fact that different intermolecular and intramolecular isotope effects were observed for **6** requires that, if one reaction pathway is operative, there must be at least two steps in the mechanism of the reaction. If the step prior to proton or deuteron transfer is assumed to be fast and exothermic, then the proton/deuteron transfer step will be faster than the reverse reaction to uncomplexed species (Figure 1f). A reasonable assignment for the first step is formation of a complex between the organolithium reagent and the substrate.[17] This pathway is shown for the conversion of **1** to **2** via **3**.[18]

The fact that a small, but measurable intermolecular isotope effects was observed for the conversion of **6** and **6**-d_2 can be rationalized. First, if the rates of decomplexation and deprotonation are competitive (i.e., k_2 is not $\gg k_{-1}$), then the relative rates of decomplexation and proton or deuteron removal from **6**-d_0 and **6**-d_2 would be different. The deuterated substrate would be more likely to decomplex than the undeuterated substrate, and isotopic fractionation would occur. Alternatively, pathways that would give high intra- and intermolecuar isotope effects (Figure 1a,c,e) could be operative concurrently with pathways that give high intramolecular isotope effects and low intermolectuar isotope effects (Figure 1b,d). Complicated kinetic schemes for organolithium reactions have been reported, and should some of these pathways either not require complexation or proceed through reversible complexation, the measured intra- and intermolecular isotope effects would be different, and the intermolecular isotope effect would be greater than 1.[4c] The present work does not distinguish between these possibilities, although if multiple pathways are operative, at least one pathway must have two steps. In the abscense of additional information, a single mechanism is to be preferred over multiple mechanisms.

Quantitative evaluation of the observed k_H/k_D values in terms of the relative magnitudes of k_1, k_{-1}, and k_2 is not warranted. If the relative rates of decomplexation (k_{-1}) and deprotonation (k_2) are competitive, simplifying approximations may not be applicable, depending on the magnitude of k_1.[19] For example, a preequilibrium approximation requires that $k_2 \ll (k_{-1} + k_1)$, which may not be valid in these systems. Alternatively, if there is more than one reaction pathway available, the kinetic scheme is more complicated than we have shown.[4c]

The correspondence of the isotope effects for proton and deuteron transfers of **7** and **8** does not allow a definitive determination to be made between one-step and two-step processes. However, the results do establish that the energy profile of the major reaction pathway is not described by the profiles in Figure 1b or d. Reasonable rationales for the differences in the comparative isotope effects in **6** vs **7** and **8** can be suggested. If a complex formed between the *N*-lithio species from **6** and *sec*-BuLi is especially stable, the barrier for reversal could be higher than the barrier for benzylic lithiation. Alternatively, the barrier for the transfer of a benzylic proton from the complex from **6** could be smaller than the barrier for transfer of the aromatic protons from complexes involving **7** and **8**. If the deprotonations of **6**, **7**, and **8** proceed through similar mechanisms, then the reactions of **7** and **8** are best described by the energy diagram of Figure 1e. Complexation between the organolithium base and the directing group is a fast, reversible process, followed by a much slower deprotonation step. In view of the extensive evidence for lithium heteroatom complexation, we believe complexation to be the more reasonable pathway.[1a]

The advantage of competitive intermolecular and intramolecular hydrogen/deuterium isotope effects for mechanistic studies is illustrated by these results. The interpretation is not obscured by the ambiguous nature of the structure of the lithiating reagent in solution or the role of TMEDA.[20] As long as the labeled and unlabeled materials react by the same mechanism, the results of the inter- and intramolecular cases should be comparable, because each is exposed to the identical, if unspecified, reactive species.[21]

In summary, the hydrogen transfer in the directed benzylic lithiation of **6** must proceed, at least in part, through at least a two-step mechanism. This observation is most easily understood in terms of formation of a prelithiation complex and cannot be rationalized in terms of simple stabilization of transition state by the directing group as the sole reaction pathway. Complexation is thought to be a rapid and largely irreversible process, followed by a slower deprotonation step. The mechanism of hydrogen transfer in the directed lithiations of **7** and **8** is proposed to proceed through a reversible complexation, followed by a much slower deprotonation step, although a single-step mechanism is not ruled out by the present data.

Thus, while a difference in intra- and intermolecular isotope effects can be taken to require a two-step mechanism, a correspondence of these isotope effects does not definitively distinguish between one- and two-step processes. In the absence of experimental evidence to the contrary, a reasonable view is that cases of both types exist, and reaction via a complex is most reasonable for cases in which there is independent evidence for complexation.

Experimental Section

General Methods. All reactions were performed with flame-dried or oven-dried glassware under a nitrogen atmosphere unless otherwise noted. Reagents were purchased from Aldrich and used without further purification unless otherwise noted. Solvents were purified by the usual methods or purchased as spectroscopic grade prior to use. THF was distilled from sodium/benzophenone under a nitrogen atmosphere immediately prior to use. Organolithium reagents were titrated by the method of Suffert prior to use.[22] Thin-layer chromatography was performed on Merck silica gel plates (0.25 mm) with QF-254 indicator. Visualization was accomplished by irradiation with UV light or I_2. Flash chromatography was performed using 230−400-mesh silica gel. Melting points were obtained using a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained using either a Varian U400 or U500 spectrometer in $CDCl_3$, using $CHCl_3$ as an internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in hertz. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory. Mass spectrometry was performed by the University of Illinois Mass Spectrometry Laboratory. Isotopic enrichments were calculated by the standard matrix method. Brine refers to a saturated

(17) Alternatives can be envisioned, e. g., rearrangement within an initially formed complex. Hoffmann, R. W.; Dress, R. K.; Ruhland, T.; Wenzel, A. *Chem. Ber.* **1995**, *128*, 861.

(18) Our earlier analyses of the reaction of **6**-d_0 and **6**-d_2, which treated the complex as being of higher energy than the reactant and present in a steady state, was, from the present perspective, incomplete, although the conclusions are valid.[4e] The more thorough discussion herein is more generally applicable.

(19) For a detailed evaluation of the mathematical conditions required to make simplifying approximations, see: Gellene, G. I. *J. Chem. Educ.* **1995**, *72*, 196.

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(21) Considerable efforts have been made in determining the structure of the major solution-state species of organolithium reagents. Solvent effects and the effects of co-solvents on chemical yields and regioselectivities are frequently rationalized in terms of changes in solution-state structure. Recent spectroscopic studies have shown that co-solvents do have an effect on solution state structure. The reactivities of the major and minor species in solution is an issue of continuing interest. For a recent example, see: Reich, H. J.; Green, D. P.; Medina, M. A.; Goldberg, W. S.; Gudmendsson, B. O.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201.

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aqueous solution of sodium chloride. Compounds **6**, **6**-d_1, and **6**-d_2,[4e] **7**, **8**,[23] **10**,[24] **11**,[25] 2-bromo-*N*,*N*-diiospropylbenzamide,[26] 2-bromo-*N*,*N*-isopropylbenzamide,[27] and *N*-isopropylphthalimide (**12**)[28] were prepared according to previously published procedures.

Synthesis of *N*,*N*-Diisopropylbenzamide-d_1 (7-d_1). A solution of 2-bromo-*N*,*N*-diisopropylbenzamide (1.35 g, 4.75 mmol) in 12 mL of THF was treated with *n*-BuLi (7.13 mmol, 1.5 equiv) at −78 °C. After 1 h, MeOD (1 mL) was added. After the solution warmed to room temperature, the THF was removed in vacuo and the residue extracted with Et_2O (3 × 15 mL), washed with brine, and dried over $MgSO_4$. After filtration and removal of solvent, the residue was purified by chromatography on silica (20% EtOAc/petroleum ether) to provide 993 mg (95%) of **7**-d_1 as a white solid (mp 70−71 °C, lit. mp 69.5−72 °C[22]), which was spectroscopically and chromatographically analogous to **7**. FI/MS analysis revealed 99.3% d_1, 0.7% d_0.

Synthesis of *N*,*N*-Diisopropylbenzamide-d_2 (7-d_2). A solution of **7** (1.00 g, 4.88 mmol) in 15 mL of THF was added to a solution of *sec*-BuLi (10.74 mmol, 2.2 equiv) and TMEDA (10.74 mmol, 1.62 mL, 2.2 equiv) in 30 mL of THF at −78 °C. After 15 min, MeOD (1 mL) was added. After the solution warmed to room temperature, the THF was removed in vacuo and the residue extracted with Et_2O (3 × 15 mL), washed with brine, dried over $MgSO_4$, filtered, and evaporated. The above procedure was repeated twice. The product was purified by chromatography on silica (20% EtOAc/petroleum ether) to provide 857 mg (85%) of **7**-d_2 as a white solid (mp 70−71 °C, lit. mp 69.5−72 °C[22]), which was spectroscopically and chromatographically analogous to **7**. FI/MS gave 99.4% d_2, 0.6% d_1.

Synthesis of *N*-Isopropylbenzamide-d_1 (8-d_1). A solution of 2-bromo-*N*-isopropylbenzamide (1.15 g, 4.76 mmol) in 10 mL of D_2O and 10 mL of $CDCl_3$ was stirred vigorously for 48 h. The layers were separated, and the organic layer was dried over $MgSO_4$, filtered, and evaporated to give the corresponding N−D analogue. This material was dissolved in 30 mL of THF, treated with NaH (572 mg, 3.0 equiv), and heated to reflux for 16 h. The solution was treated with *n*-BuLi (14.3 mmol, 3.0 equiv) at −78 °C. After 1 h, MeOD (2.9 mL) was added. After warming to room temperature, the solution was treated with 2 N HCl and extracted with CH_2Cl_2. After the solution was dried over $MgSO_4$ and filtered and the solvent removed, the residue was purified by chromatography on silica (30% EtOAc/petroleum ether) to provide 605 mg (77%) of **8**-d_1 as a white solid (mp 101−103 °C, lit. mp 99−103 °C[29]), which was spectroscopically and chromatographically analogous to **8**. FI/MS analysis revealed 97.0% d_1, 3.0% d_0.

Synthesis of *N*-Isopropylbenzamide-d_2 (8-d_2). A solution of **8** (1.04 g, 6.39 mmol) in 5 mL of THF was added to a solution of *tert*-BuLi (19.2 mmol, 3.0 equiv) and TMEDA (19.2 mmol, 2.89 mL, 3.0 equiv) in 20 mL of THF at −78 °C. After 15 min, MeOD (2.6 mL) was added. After warming to room temperature, the solution was treated with 2 N HCl, extracted with CH_2Cl_2, dried over $MgSO_4$, and filtered, and the solvent was removed in vacuo. The procedure was repeated twice. The residue was purified by chromatography on silica (30% EtOAc/petroleum ether) to provide 605 mg (77%) of **8**-d_2 as a white solid (mp 100−103 °C, lit. mp 99−103 °C[28]), which was spectroscopically and chromatographically analogous to **8**. FI/MS analysis revealed 99.6% d_2, 0.4% d_1.

Synthesis of 1,3-Dimethyl-5-phenylimidazolidine-2,4-dione (9). A solution of **6** (327 mg, 1.83 mmol) and TMEDA (5.50 mmol, 0.83 mL, 3.0 equiv) in 20 mL of THF was treated with *sec*-BuLi (5.50 mmol, 3.0 equiv) at −78 °C. After 1 h, CO_2 was bubbled through the solution. Water was added to the solution after 15 min and allowed to warm to room temperature. The solution was extracted with CH_2Cl_2 and dried over $MgSO_4$. After filtration and evaporation, the residue was chromatagraphed on silica (50% EtOAc/petroleum ether) to provide 333 mg (82%) of **9** as a white solid (mp 100−101 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.89 (s, 3H), 3.06 (s, 3H), 4.79 (s, 1H), 7.23−7.27 (m, 2H), 7.40−7.42 (m, 3H); ^{13}C ($CDCl_3$, 125 MHz) δ 25.2, 28.1, 65.9, 127.2, 129.3, 132.5, 156.9, 171.3; FI/MS (M^+) 204. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.38; H, 5.97; N, 13.83.

Procedure for Determination of Intramolecular Isotope Effects. A ca. 0.05 M solution of **6**-d_1, **7**-d_1, or **8**-d_1 in THF was treated with a solution of TMEDA (2.2, 1.1, and 2.2 equiv, respectively) and *sec*-BuLi (2.2, 1.1, and 2.2 equiv, respectively) in THF at −78 °C in a cold transfer flask. After 15 min, anhydrous CO_2 was bubbled through the solution for at least 15 min. After warming to room temperature, the solution was treated with 2 N HCl, extracted with CH_2Cl_2, and dried over $MgSO_4$. Filtration and evaporation gave the corresponding products **9**, **10**, or **11**, which were separated from the starting materials chromatographically on silica (EtOAc, 3% MeOH/CH_2Cl_2, and 5% MeOH/CH_2Cl_2, respectively) Mass recoveries were typically better than 80%. Carboxylic acids **10** and **11** were converted to *N*-isopropylphthalimide (**12**) prior to characterization.[24] Mass spectrometry was performed on the recovered **6**, **7**, and **8** as well as the products **9** and **12**, and the ratios of **9**−**11**-d_1 to **9**−**11**-d_0 were calculated.

Procedure for Determination of Intermolecular Isotope Effects. A ca. 0.05 M solution of known mixtures of **6**-d_0/**6**-d_2, **7**-d_0/**7**-d_2, or **8**-d_0/**8**-d_2 in THF was treated with a solution of TMEDA (1.2−1.8, 0.25−0.9, and 1.2−1.8 equiv, respectively) and *sec*-BuLi (1.2−1.8, 0.25−0.9, and 1.2−1.8 equiv, respectively) in THF at −78 °C in a cold transfer flask. After 15 min, anhydrous CO_2 was bubbled through the solution for at least 15 min. After warming to room temperature, the solution was treated with 2 N HCl, extracted with CH_2Cl_2, and dried over $MgSO_4$. Filtration and evaporation gave the corresponding products **9**, **10**, or **11**, along with starting materials, which were separated chromatographically on silica (EtOAc, 3% MeOH/CH_2Cl_2, and 5% MeOH/CH_2Cl_2 respectively). Yields and mass balances were calculated from isolated materials. Mass recoveries were typically better than 80%. Carboxylic acids **10** and **11** were converted to **12** prior to characterization. Mass spectrometry was performed on the recovered **6**, **7**, and **8**, as well as the products **9** and **12**, and the extents of conversion of **6**−**8**-d_0 to **9**−**11**-d_0 and **6**−**8**-d_2 to **9**−**11**-d_1 were calculated.

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Supporting Information Available: Sample calculations for isotope effects and evaluation of error propagation (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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