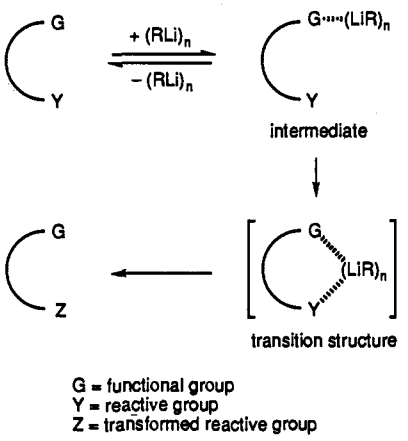
Complex-Induced Proximity Effects: Evidence for a Complex on the Reaction Pathway of α′-Lithiation of a Benzylic Urea

James E. Resek and Peter Beak*

Department of Chemistry, Roger Adams Laboratory
University of Illinois, Urbana-Champaign
Urbana, Illinois 61801

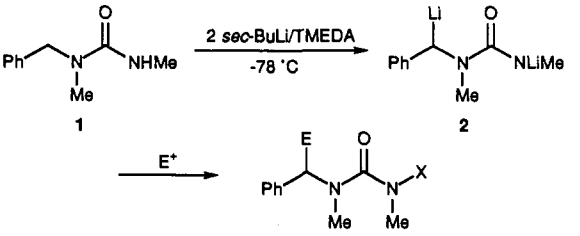
Received September 3, 1993

The possibility that prelithiation complexes are intermediates on the reaction pathway of directed lithiations has been recognized almost since the earliest reports of these reactions.[1,2] In an extension of that concept, it has been suggested that a variety of novel and useful reactions of organolithium compounds can be understood to proceed through an initial complex which has a proximity between the organolithium reagent and the reactive group Y that entropically and enthalpically induces a kinetically favorable transition structure leading to the product.[2c] Many examples of the complex induced proximity effect (CIPE) involve lithiations, and this process is illustrated for the conversion of functionality Y to Z.[2-5]



The heuristic value of this concept is well-established, but definitive evidence for the pathway has been limited. We have observed the presence of a complex in an α′-lithiation of an amide and provided a kinetic analysis consistent with its intermediacy.[4b] Collum has discussed a kinetic criterion for CIPE and reported cases which do and do not conform.[5] Meyers and Dickman have reported an α-lithiation of a chiral formamidine dihydroisoquinolone derivative which exhibits no hydrogen–deuterium isotope effect, a result consistent with rate-determining formation of a prelithiation complex, and Meyers *et al.* have provided additional isotope effect studies which support that interpretation.[6] We now report a study of the α′-lithiation of *N*-benzyl-*N*,*N*′-dimethyl urea (**1**) using intramolecular and intermolecular hydrogen–deuterium isotope effects to address the question of whether there is a prelithiation complex on the reaction pathway.[7,8]

The overall substitution of **1** is illustrated by its treatment with *sec*-BuLi/TMEDA at −78 °C to give **2**, followed by reaction with electrophiles to give the products **1**-d_1, **3**, and **4**.



1-d_1, E = D, X = H, 90% (95% d_1)
3, E = TMS, X = H, 83%
4, E = Me, X = Me, 91%
5, E = H, X = Me

The intramolecular isotope effect for the formation of **2** was determined by treatment of **1**-d_1 (2.7% d_2, 95.0% d_1, 2.3% d_0) with 1.8 equiv of *sec*-BuLi/TMEDA for 60 min at −78 °C followed by dimethyl sulfate to give the α′-substitution product **4**. The product of undilithiated starting material was obtained as **5**. Field ionization mass spectrometric (FIMS) analysis of the isotopic composition of the product mixture indicates that the reaction has $(k_H/k_D)_{intra} = 13 \pm 3$.[9] The intermolecular isotope effect was measured for reaction of a *ca.* equimolar (46.3% d_2, 0.7% d_1, 53.0% d_0) mixture of **1** and **1**-d_2 and provides a product mixture with an isotopic composition consistent with $(k_H/k_D)_{inter} = 2.0 \pm 0.7$. The fact that two unequal isotope effects are observed requires a reaction pathway which has at least two steps.

The most straightforward way to account for the observed isotope effects is to consider the mechanism to involve formation of a prelithiation complex **6** from the *N*-lithiourea **7** and *sec*-BuLi, followed by irreversible proton removal to give the dilithiated urea **2** (Scheme 1).[10] Under this mechanism, relationships between the observed isotope effects and the rate constants of the steps can be derived by assumption of the steady-state approximation for the complex **6**. This analysis for **7**-d_1 shows that the observed intramolecular isotope effect, as measured by the ratio of products from **2** and **2**-d_1, is equal to the ratio of the rates of the proton and deuterium removal steps and thus is equal to the actual isotope effect k'_H/k'_D for this step. Neither the identity of the rate-determining step nor the potential presence of several pre-steady-state equilibria affects this conclusion, assuming proton and deuterium removal result from the same complex.

For the intermolecular isotope effect, the relationship of the product ratio of **2** and **2**-d_1, $(k_H/k_D)_{inter}$, to the actual isotope

(1) Gilman [Gilman, H.; Morton, J. W. *Org. React.* **1954**, *8*, 258] credits Roberts and Curtin [Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658] with demonstrating this effect in directed ortho lithiations.

(2) (a) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (c) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (d) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(3) For some recent examples, see: (a) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 789. (b) Petasis, N. A.; Teets, K. A. *Tetrahedron Lett.* **1993**, *34*, 805. (c) Bridges, A. J.; Lee, A.; Maduakor, E. C.; Schwartz, C. E. *Tetrahedron Lett.* **1992**, *33*, 7595. (d) Guijarro, A.; Ramón, D. J.; Yus, M. *Tetrahedron* **1993**, *49*, 469. (e) Hoffmann, R. W.; Brumm, K.; Bewersdorf, M.; Mikolaiski, W.; Kusche, A. *Chem. Ber.* **1992**, *125*, 2741 and references cited therein. (f) For a discussion of the role of complexes in ortho lithiations and further references, see: Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628.

(4) The enthalpic component is considered to arise from increased reactivity due to coordination with the lithium: (a) Bartlett, P. D.; Gobel, C. V.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 7425. (b) Hay, D.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145–8153.

(5) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008.

(6) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263–1265. Warmus, J. S.; Rodkin, M. A.; Barkley, R.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1993**, 1357.

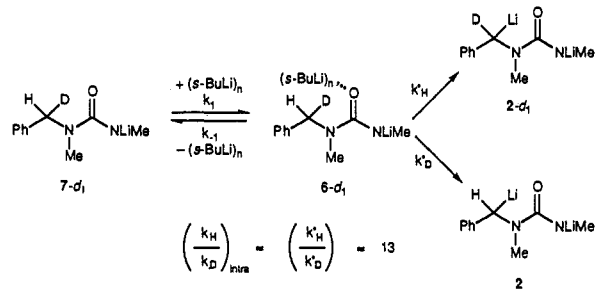
(7) Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126–8134 and references cited therein. In this context, intra- and intermolecular refer to the locations of the proton and deuterium on the organic substrate and not to differences in reaction mechanism.

(8) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607–3614. Cheng, C.; Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1984**, *49*, 2910 and references cited therein.

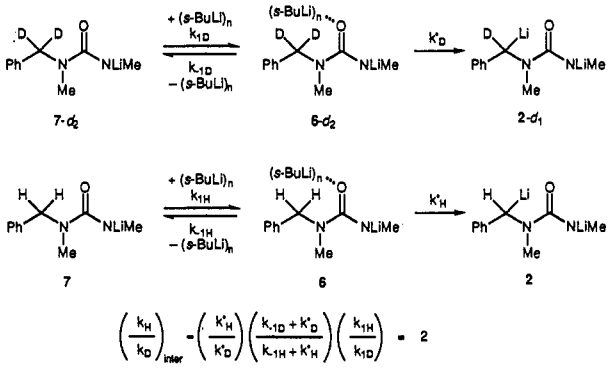
(9) The specific value of the intramolecular isotope effect is highly dependent upon the amount of **1**-d_0 present in the starting material. FIMS analysis of **1** indicated 2.3% d_0, and this amount provides $(k_H/k_D)_{intra} = 13.2 \pm 1.3$. However, this amount of **1** is subject to a relatively large error, *e.g.*, use of 3.0% **1**-d_1 starting material in the calculation provides an isotope effect of 16.5. An absolute lower limit of the intramolecular isotope effect of 8.1 is calculated if no **1**-d_0 is considered to be present in the starting mixture. We consider the FIMS analysis to be accurate to a level which allows an error assignment of ±3. In any case, it is clear that the intramolecular and intermolecular isotope effects are substantially different.

0002-7863/94/1516-0405$04.50/0

Scheme 1. Intramolecular Hydrogen–Deuterium Isotope Effect



Scheme 2. Intermolecular Hydrogen–Deuterium Isotope Effect



effect for hydrogen transfer is more complex.[7] Steady-state treatment for a mixture of **7** and **7-d_2** gives an expression for $(k_H/k_D)_{inter}$ which involves the rate constants for the formation and decomplexation of the putative complex as shown in Scheme 2. Two limiting reaction profiles exist. If the hydrogen removal step is rate determining, $k_{-1H} \gg k'_H$ and $k_{-1D} \gg k'_D$ in the extreme case. In this situation, k_{-1H} and k_{-1D} dominate the middle term of the expression for the intermolecular isotope effect. If the reasonable assumption is made that the isotopic substitution does not affect the complexation rates, *i.e.*, $k_{1H} = k_{1D}$ and $k_{-1H} = k_{-1D}$, then the intermolecular isotope effect reduces to $(k_H/k_D)_{inter} = k'_H/k'_D$, the actual isotope effect. In the other limit, if complexation is the slow step of the reaction, then $k_{-1H} \ll k'_H$ and $k_{-1D} \ll k'_D$. In this situation, k'_H and k'_D dominate the middle term of the expression, and the intermolecular isotope effect reduces to $(k_H/k_D)_{inter} = k_{1H}/k_{1D} \cong 1$. Thus, under this mechanism, the experimentally determined value of the intermolecular isotope effect can lie anywhere between the true isotope effect, k'_H/k'_D, and unity, depending on the relative rates of the reactions involved in the partitioning of **6**. A difference between the intramolecular and intermolecular isotope effects can be taken to show that both steps of the reaction can have an effect on the observed rate.

The expression for $(k_H/k_D)_{inter}$ can be used to calculate the required ratio of rate constants for the partitioning of **6** to give the observed experimentally measured effects, if secondary isotope effects are ignored. If $k_{-1H} = k_{-1D} = 1.2\ k'_D = 0.09$, then k'_H isotope effects consistent with the observations are obtained. This suggests that the formation of the reactive complex **6** and proton removal are competitive in the reaction. In the specific case of **1**, which most closely resembles the situation in a synthetic application of this reaction, the barrier to deprotonation of **6** can be calculated to be 0.9 kcal/mol lower than that for its formation from **7** and *sec*-BuLi. In the case of **1-d_2**, the barrier to deuterion removal can be calculated to be 0.06 kcal higher than decomplexation. An alternative mechanism, in which initial complexation occurs on all encounters of **1** with an aggregated organolithium and is largely irreversible within an aggregated species until after dilithiation is complete, could also fit these observations. That possibility is not completely ruled out by our observation that the reaction is only *ca.* 5% complete 5 s after mixing.

In any case, the principle definitive conclusion which can be drawn from these results is that the conversion of **7** to **2** requires a reaction pathway that has at least two steps. The mechanism shown to involve **6** provides these steps in a way that is consistent with a prelithiation complex on the reaction pathway for the directed lithiation of **1**. These results may be considered to provide support for the role often suggested for complexes in related reactions.[1-6,10]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for financial support of this work.

Supplementary Material Available: Experimental details for the preparation of **1**, **1-d_1**, **1-d_2**, **3–5**, and the measurement of isotope effects, calculations of isotope effects, and derivations of kinetic expressions (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) The conclusions are not compromised by the fact that **6** and **7** are representative of the more aggregated species which may exist in pre-steady-state equilibria under the reaction conditions.