

Kinetic Isotope Effects in the Deprotonation of Chiral Formamidines

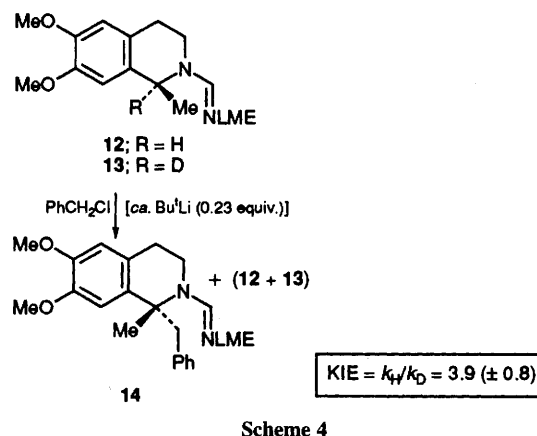
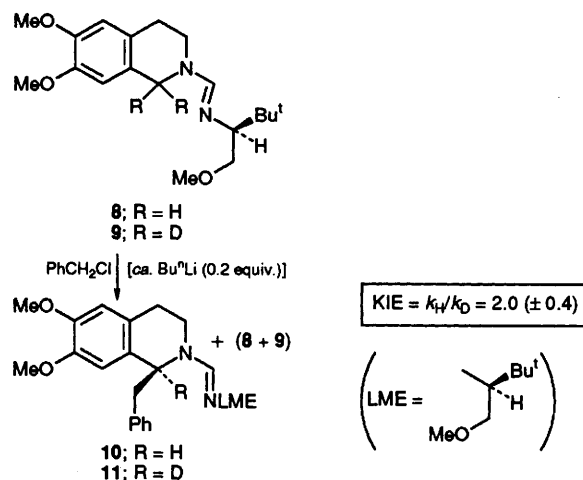
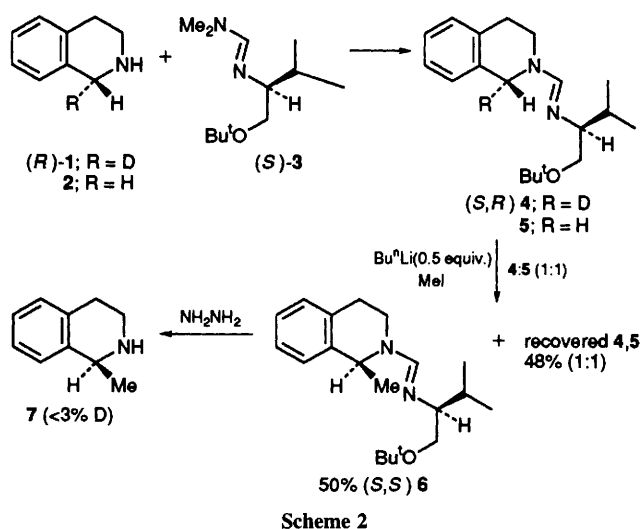
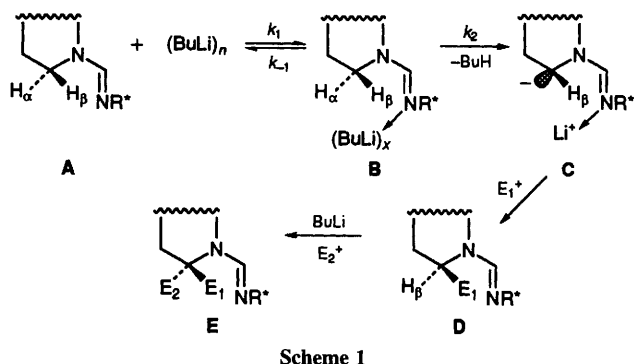
Joseph S. Warmus, Mikhail A. Rodkin, Robert Barkley and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

Metallation of 6,7-dimethoxy isoquinoline formamidines show a kinetic isotope effect, in contrast to the metallation of the 6,7-dihydro system; the isotope effect for the secondary proton in the dimethoxy system is smaller than usual (2.0) while the isotope effect for tertiary proton removal is somewhat larger (~4.0), this is explained by the magnitude of pK_a on isotope effect as well as competition between the pre-complexation step and the deprotonation step.

We have previously described the metallation-alkylation of chiral and achiral formamidines to mono- and di-alkylated derivatives (**D**, **E**) which has led to a variety of alkaloids, amines and related systems.^{1,2a} However, efforts to fully understand the mechanistic aspects of this process² continue and the currently accepted overall picture is shown in Scheme 1. We presently believe that the formation of complex **B** is the rate-determining step³ followed by a rapid deprotonation of H_α to give **C**. The configuration of the alkylated product **D** has

been confirmed by experiment and rationalized from a computational analysis of the various conformers of **C**.^{2b} Further metallation of **D** revealed that the proton is again removed only when it is α -disposed² (as in **B**) and the alkylation, leading to **E**, occurs predominantly from the α -face (X-ray determination).² We also determined that in the absence of the chiral auxiliary (**R***) the configurational stability of the lithio carbanion **C** deteriorates rapidly.^{4,5} This supports the conclusion that the configuration of anion **C** is the



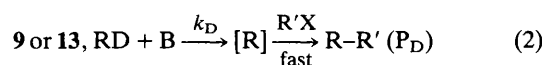
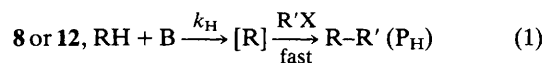
result of thermodynamic stability, rather than a kinetically controlled conformation.⁶

In an earlier study³ using the deoxy dihydroisoquinolines **1** and **2**, we transformed these into the corresponding chiral isoquinolines **4** and **5** using the chiral auxiliary **3**. The original question asked was: is there a preference for H or D removal in **4** and **5**? When a 1 : 1 mixture of **4** and **5** was treated with 0.5 equiv. of BuⁿLi, **6** was expectedly obtained in 50% yield containing less than 3% deuterium (Scheme 2). The remaining **4** and **5** were recovered showing the same ratio of D/H as the starting material. Our conclusion, therefore, was simply that the deprotonation step in Scheme 1 (k_2) was not rate-determining. Perhaps the deaggregation of butyllithium to form the complex (k_1 , Scheme 1) was the most likely rate-controlling step since it is presently difficult to find another option. The next question to be asked was: If the pK_a of the proton in **4** or **5** was decreased, would the deprotonation step become rate determining?

We have now examined the methoxy substituted systems **8** and **9**⁷ and found, in contrast to **4** and **5**, the recovered mixture of starting materials in the competitive metallation was enriched with deuterated isotopomer. This now suggests that a kinetic isotope effect was indeed present. In order to obtain the value of the isotope effect (KIE), competition experiments were performed under pseudo-first-order conditions. An approximately equimolar mixture of **8** and **9** was metallated by *n*-butyllithium (0.2 equiv.) as the limiting reagent at -78°C in tetrahydrofuran (THF); subsequent alkylation with benzyl chloride gave a mixture of **10** and **11** and recovered **8** and **9** (Scheme 3). Because of the low conversion ($\sim 20\%$) we were unable to assess the D/H ratio in **10/11** from NMR or mass spectral techniques with any reasonable accuracy although there was generally a higher proportion of H than D (**10** > **11**).

A more accurate D/H assessment could be obtained using mass spectrometry from the recovered **8** and **9**. Furthermore, any effort to accurately assess H/D ratios in **10/11** would not be useable in the second alkylation (to **14**) since the carbon possessed no proton. Therefore, we felt secure in analysing the H/D ratios for recovered, unreacted starting materials **8**, **9** and **12**, **13** (*vide infra*). Furthermore, we examined the possibility of crossover experiments which would shed doubt on the observed H/D ratios. None were found after several experiments using lithio-**8** and deuterio-**9**.

In such competition experiments [presented in general form by eqns. (1) and (2)] the ratio of products derived from protio (P_H) and deuterio substrates (P_D) should be determined by $[P_H]/[P_D] = k_H[RH]_0/k_D[RD]_0$, where $[RH]_0$ and $[RD]_0$ are the starting concentrations of protio and deuterio substrates. Then isotope effect (KIE) = $k_H/k_D = [P_H][RD]_0/[P_D][RH]_0$. As already stated, the low conversion to products (required for pseudo-first-order conditions) precluded any useful NMR assessment. However, mass spectra data gave accurate H/D ratios for methoxy-substituted formamidines **8/9** before and after the reaction.



The expression for isotope effect (KIE) can be arranged into eqn. (3)

$$\text{KIE} = \frac{(C + FC - S + F)}{(S - F + CS + CSF)} \times S \quad (3)$$

where $S = [\text{RD}]_o/[\text{RH}]_o$ (ratio of the starting materials before reaction); $F = [\text{RD}]_f/[\text{RH}]_f$ (ratio of the starting materials after reaction); $C = P_H + P_D/[\text{RH}]_f + [\text{RD}]_f$ (ratio of the products to the remaining starting material).

The F and S values and their uncertainties were obtained from the experimental mass spectra.† The C value was obtained by GC and used assuming an uncertainty of 5%.

After two runs, a kinetic isotope effect was calculated to be $2.0 (\pm 0.4)$. The smaller than expected isotope effect noted in the metallation of **8** and **9** prompted us to further examine the magnitude of this effect in the more energy demanding tertiary proton removal. Once again, an approximately equimolar mixture of protio and deuterio formamidines **12** and **13** was treated (THF, -78°C) with a deficiency (0.23 equiv.) of *tert*-butyllithium (Scheme 4). Neither Bu^nLi or Bu^sLi were sufficiently strong bases to remove the tertiary proton (or D) in **12** or **13**. Since both formamidines gave **14** (*i.e.* P_H and P_D products are identical), the calculation of isotope effect was based again on the initial and final ratio of **12** and **13** (eqn. 3) as determined by mass spectroscopy. Using eqn. (3), the average kinetic isotope effect observed for **12** and **13** was found to be $3.9 (\pm 0.8)$,⁸ considerably higher than in **8** and **9**. We may conclude that the sequence depicted in Scheme 1 is consistent with the results obtained. It shows that when the pK_a of the protons in question is increased, the removal of the proton in **B** is not as facile and the reverse reaction (back to **A**) now becomes more significant; *i.e.* k_1 can compete with k_2 . The presence of methoxy groups in **8/9** and **12/13** sufficiently lowers the acidity over **4/5** such that not every complexation to **B** leads to rapid deprotonation and k_2 is no longer $\gg k_{-1}$. As proposed earlier for **4** \rightarrow **6**, the rate-limiting step may be k_1 , showing no kinetic isotope effect. In **8/9** \rightarrow **10/11** and **12/13** \rightarrow **14** the rate is affected by k_2 as well as by k_1 , so a kinetic isotope effect, albeit diminished, is observed. The increase in isotope effect, 2.0 for **8/9** and 4.0 for **12/13**, may be the result of the poorer kinetic acidity in the latter and this has been discussed by Melander.⁹ This metallation behaviour and subsequent alkylations continue to provide further opportunities for synthetic advances in asymmetric molecular construction.

† Experimental mass spectra were analysed using an over-determined least-squares program, developed in the group of Professor J. R. Norton.

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