$^{13}$C Kinetic Isotope Effects for the Addition of Lithium Dibutylcuprate to Cyclohexenone. Reductive Elimination Is Rate-Determining

Doug E. Frantz,[†] Daniel A. Singleton,*,[†] and
James P. Snyder*,[‡]

Department of Chemistry, Texas A&M University
College Station, Texas 77843
Department of Chemistry, Emory University
Atlanta, Georgia 30329

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The conjugate addition of lithium dialkylcuprates to enones is a vital tool in synthetic organic chemistry. Despite the broad use of these reactions and abundant effort, a clear mechanistic picture has yet to be delineated. Early studies by House suggested a single-electron-transfer mechanism based on a correlation between the reduction potentials of enones and their reactivity in conjugate additions.[1] Later studies have tended to focus on copper−olefin π-complexes[2] as key intermediates, although lithium−enone complexes,[3] charge-transfer complexes,[4] α-cuprio ketones,[5] and h^3-allyl complexes[6] have all been proposed to be important. Most mechanistic proposals finish with the formation of a "Cu^{III}" intermediate followed by reductive elimination to form the product enolate. Although recent work has shown the plausibility of a ligated formal Cu^{III} (with a Cu^I-like electronic distribution),[7] a weak point is a lack of direct evidence for these normally high-energy species.
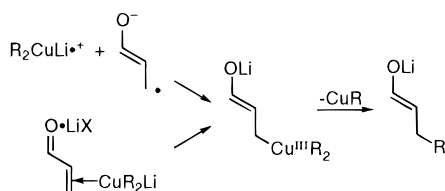
For any reaction, knowledge of the rate-determining step is key to an understanding of reactivity and selectivity. To gain focused information on the rate-determining step for cuprate conjugate additions, we have determined here a complete set of ^{13}C kinetic isotope effects (KIEs) for the prototypical reaction of Bu$_2$CuLi with cyclohexenone. The results implicate rate-determining reductive elimination from Cu and have broad implications for both synthetic and mechanistic studies of cuprate conjugate additions.

The ^{13}C KIEs for cyclohexenone in its reaction with Bu$_2$-CuLi were determined by recently reported methodology for the combinatorial high-precision determination of small KIEs at natural abundance.[8] Reactions of natural abundance cyclohexenone on a 0.2 mol scale were taken to 91.0, 92.1, and 81.1%

completion by the rapid addition of Bu$_2$CuLi (prepared from *n*-BuLi + CuBr·SMe$_2$) in THF to vigorously stirred solutions of cyclohexenone in THF at −78 °C. The reactions were quenched at −78 °C, and the unreacted cyclohexenone[9] was recovered by an extractive workup followed by column chromatography. The recovered cyclohexenone was analyzed by ^{13}C NMR[10] compared to a standard sample of cyclohexenone from the same commercial lot. The changes in ^{13}C isotopic composition were calculated using C$_6$ as an "internal standard"[11] assuming that its isotopic composition does not change during the reaction. From the changes in isotopic composition, the KIEs and errors were calculated by the previously reported method.[8]

The ^{13}C KIEs for the butyl group were determined by analysis of the product from reactions taken to low conversion, in a simple novel manner. Reactions of ≈0.2 mol of natural-abundance Bu$_2$CuLi in THF at −78 °C were taken to ≈10% conversion by the addition of 20 mmol of cyclohexenone. The quantitatively-formed 3-butylcyclohexanone was isolated after an extractive workup by chromatography. An NMR standard sample of 3-butylcyclohexanone was prepared by the addition of BuLi (from the same bottle as that used to form the Bu$_2$-CuLi) to excess 3-ethoxy-2-cylohexen-1-one followed by hydrolysis (1 N HCl) and hydrogenation (H$_2$/Pd/C). The two samples of 3-butylcyclohexanone were compared by ^{13}C NMR, and the ^{13}C KIEs were calculated directly from the change in integrations relative to C$_c$ as internal standard.[11] The precision of KIEs determined in this manner (±0.4−0.7%) is limited by the reproducibility of NMR integrations but is sufficient for chemical interpretability for the purpose at hand.

The resulting KIEs ($^{12}k/^{13}k$) are summarized in Table 1. The appreciable KIE at C$_3$ (1.020−1.026) is strongly indicative of a substantial bonding change at C$_3$ in the rate-limiting step. The significant KIE at C$_a$ of the butyl group (1.011−1.016), though relatively small, suggests that C$_a$ is also undergoing a bonding change, i.e., the butyl group is being transferred in some fashion, in the rate-limiting step. Taken together, these results implicate reductive elimination as the rate-determining step.[12,13]

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(9) In a control reaction taken to completion, <1% cyclohexenone was detected after quenching. This indicates that the recovery of cyclohexenone from reactions taken to ≈90% conversion was not simply the result of enolization.

(10) As described in the Supporting Information, a number of precautions were taken to minimize both random and systematic errors in the NMR analysis. See: Rabenstein, D. L.; Keire, D. A. In *Modern NMR Techniques and Their Application in Chemistry*; Popov, A. I., Hallenga, K., Eds.; Marcel Dekker: New York, 1991; pp 323−69. Samples from recovered and standard material were prepared identically and a T_1 determination was carried out for each sample. ^{13}C spectra were obtained with inverse-gated ^{1}H decoupling and a 120 s delay between calibrated $2\pi/9$ pulses.

(11) C$_6$ of cyclohexenone and C$_c$ of butylcyclohexanone were chosen as internal standards because their ^{13}C peaks were most cleanly separated from other peaks in the ^{13}C NMR and potential impurities. Small deviations from KIEs of 1.000 for these carbons will not affect the conclusions.

(12) Corroborative evidence for rate-limiting reductive elimination comes from the observation of enone *Z*−*E* isomerization (see ref 2b), although other isomerization mechanisms are possible, and a linkage between the isomerization and the reaction process had not been established. House had earlier used the same evidence to support an electron-transfer mechanism: House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975,** *97,* 2778.

(13) A referee suggested that the butyl group KIEs could be the result of an internal competition between butyl groups, after the rate-limiting step, in a structure such as **A**.
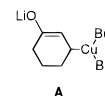
Such a competition would not be expected if the butyl groups were diastereotopic in a square-planar structure such as **3** (see ref 7). However, we have addressed this question experimentally by determining the KIEs for the reaction of cyclohexenone with BuCuCNLi. The observed KIEs were C$_a$ 1.020(4); C$_b$ 1.000(5); C$_c$ 1.000 (assumed); C$_d$ 1.005(4). In this case no internal competition is possible, and the large C$_a$ KIE must be the result of the rate-limiting step.

[†] Texas A&M University.
[‡] Emory University.
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Table 1. ^{13}C KIEs ($^{12}k/^{13}k$) for the Addition of Bu$_2$CuLi to Cyclohexenone (-78 °C)
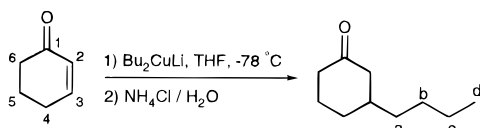
KIEs based on starting material[a,b]	experiment		
	1	2	3
C$_1$	1.004(2)	0.999(2)	1.002(5)
C$_2$	1.006(2)	1.005(2)	1.005(3)
C$_3$	1.026(2)	1.020(4)	1.024(4)
C$_4$	0.999(3)	0.998(3)	0.998(3)
C$_5$	1.002(2)	1.005(3)	1.009(4)
C$_6$	1.000 assumed[d]		

KIEs from product[b,c]	experiment		
	4	5	6
C$_a$	1.016(4)	1.011(4)	1.015(4)
C$_b$	0.999(4)	0.993(4)	0.997(4)
C$_c$	1.000 assumed[d]		
C$_d$	1.002(7)	1.003(7)	1.002(7)

[a] Experiments 1−3 are reactions carried to 91.0(8), 92.1(7), and 81.1(1.4)% completion, respectively, to determine the KIEs for cyclohexenone. [b] Standard deviations are shown in parentheses. [c] Experiments 4−6 are reactions carried to ≈10% completion to determine the KIEs for the incoming butyl group. [d] See ref 11.

Theoretical calculations were used to place the interpretation of these results, particularly the smaller C$_a$ KIE, on a stronger basis. The previously reported[7] structures **1**, **3**, and **4** and the new transition structure **2**, all obtained with DFT calculations at the Becke3LYP/LANL2DZ level, were used as models for possible transition states in cuprate conjugate addition. Theoretical kinetic or equilibrium ^{13}C isotope effects at −78 °C were calculated[14] for **1−4**, using as calculational starting materials Me$_2$Cu$^-$ for the methyl groups and ethylene for the other carbons in **2**. The results are shown below.

Structure **1** is a transition structure for reductive elimination from a square planar intermediate **3** derived by solvent addition to the precursor π-complex **4**.[7] The KIEs predicted for **1** are in excellent agreement with those experimentally observed for

C$_a$ of the butyl group. Structure **2** is a transition structure for the 1,2-addition of a Cu−Me bond across the C=C bond of ethylene, modeling the proposed formation of an α-cuprio ketone. On the basis of this structure, substantial KIEs would be expected for C$_a$ of the butyl group and for both C$_2$ and C$_3$ of the enone. The observed small KIE for C$_2$ would seem to exclude the direct formation of an α-cuprio ketone.[15] Structures **3** and **4** were used as models for rate-limiting Michael addition of Cu to the β-carbon of an enone and rate-limiting formation of a π-complex, respectively. Although **3** and **4** are intermediates, not transition structures, the equilibrium KIEs for formation of **3** and **4** should roughly model the *secondary* KIEs expected if these steps were rate limiting, since the methyl groups are not being transferred in these steps. The predicted slightly inverse KIEs indicate that these steps cannot account for the observed C$_a$ KIE.

The observed KIEs are also inconsistent with rate-limiting electron transfer. An electron-transfer step in the mechanism prior to reductive elimination cannot be ruled out. However, the central evidence for the importance of electron transfer—the correlation of reactivity with reduction potential—is compromised because it is the energy of the transition state for the rate-limiting step that determines reactivity. It is also clear that studies trying to understand or control the stereochemistry of cuprate conjugate additions should focus on the reductive elimination step.

The mechanism of cuprate reactions is often thought to depend on cuprate structure, substrate, solvent, additives (e.g., TMSCl), and the detailed reaction conditions. We anticipate that kinetic isotope effects will prove a powerful tool in delineating the mechanistic differences.

Supporting Information Available: Procedures for reactions, NMR measurements, and KIE calculations, and the energy, coordinates, and frequencies for the new calculated structures (15 pages). See any current masthead page for ordering and Internet access instructions.

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(15) A transition state similar to **2** (see supporting information) was found for the addition of the neutral aggregate (CH$_3$)$_2$CuLi·LiI to ethylene, for which similar KIEs are predicted (1.026 for the methyl group undergoing addition, 1.033 and 1.034 for the ethylene carbons).