

Opening the ‘black box’: oscillations in organocuprate conjugate addition reactions†‡

Michael D. Murphy,^a Craig A. Ogle^{*a} and Steven H. Bertz^{*b}

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Under the conditions of a rapid injection experiment, the conjugate addition reactions of butyl Gilman reagents with 2-cyclohexenone undergo oscillations of a complex nature.

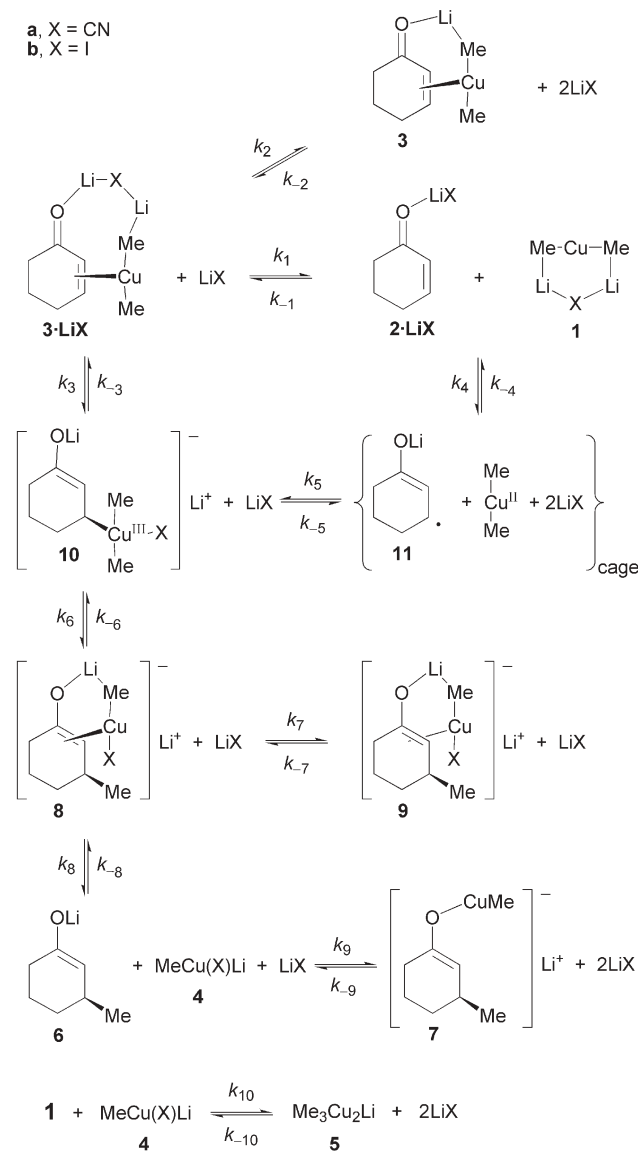
Oscillating chemical reactions were considered an impossibility, and then a scientific curiosity—until they were discovered in living systems.¹ Noyes has classified oscillating reactions into five broad types,² and Epstein has constructed a detailed taxonomy of the major class, homogeneous redox oscillators (e.g., the Belousov–Zhabotinsky reaction).¹ Oscillatory behavior has not been reported for the ‘textbook’ chemical reactions used by synthetic chemists to prepare complex natural products and pharmaceuticals. By using rapid-injection nuclear magnetic resonance (RI-NMR) techniques,^{3,4} we have been able to observe oscillations in the House–Whitesides reaction, the extremely useful β -alkylation of α,β -unsaturated carbonyl compounds mediated by organocuprates (Gilman reagents).^{5–9}

RI-NMR spectroscopy is an ideal technique for preparing oxygen-sensitive and thermally unstable reaction mixtures, such as the ones discussed herein, at low temperatures in the dry nitrogen atmosphere of a temperature-controlled NMR probe.^{3,4} Subsequent reactions can be followed by using standard NMR techniques, e.g., intermediates can be characterized by their spectra, and the rates at which species appear and disappear can be measured by integration of suitable peaks.

Thus, we treated $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$ **1a** and $\text{Me}_2\text{CuLi}\cdot\text{LiI}$ **1b** with **2** in THF-d_8 at -100°C , assigned structures to the initial π -complexes **3**·LiCN and **3**·LiI (Scheme 1), respectively, and measured their rates of formation and dissociation to salt-free π -complex **3**.⁴ In contrast to the smooth first and second order kinetics observed for these processes at -100°C , the plots for the reactions at temperatures between -50 and -70°C , where they are used synthetically, do not fit a simple kinetic scheme.

Fig. 1 shows the plots of concentration vs. time for the major species in the reaction mixture prepared from **1a** (2 equiv.) and **2** in THF-d_8 at -70°C , and Fig. 2 shows the corresponding plots for **1b** and **2**. Figs. 3 and 4 contain the stacked plots of the ^1H NMR spectra upon which Figs. 1 and 2 are based.

The most dramatic oscillations are in the concentration of **2** (\blacktriangle , vinyl H peaks at 5.9 and 7.0 ppm). In the reaction with **1a**, there are several oscillations in the interval 0–200 s, and damped oscillations continue with decreasing amplitude and increasing period until the reaction is complete. In the reaction with **1b**, there are two oligo-oscillations¹⁰ before monotonic decay. A crucial observation is that in each case the concentration of **2** initially



Scheme 1

† Electronic supplementary information (ESI) available: experimental methods and concentration vs. time plots at -60°C . See <http://www.rsc.org/suppdata/cc/b4/b412514b/>

‡ The title is an allusion to that of a critical review, ‘Decoding the ‘Black Box’ Reactivity That Is Organocuprate Conjugate Addition Chemistry’.⁸ Limited oscillations such as we observe are sometimes called ‘oligo-oscillations’.¹⁰

*cogle@email.uncc.edu (Craig A. Ogle)

sbertz@complexitystudycenter.org (Steven H. Bertz)

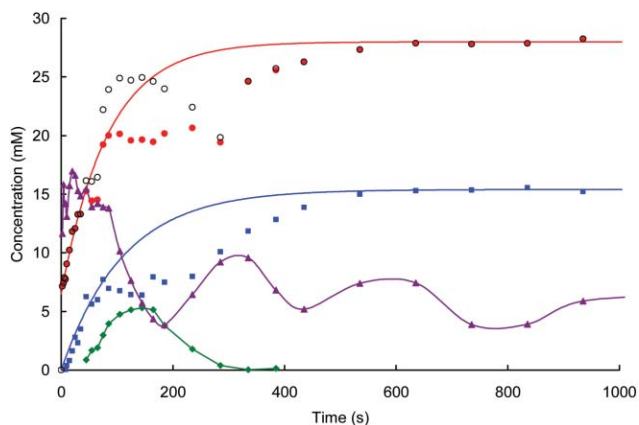


Fig. 1 Concentration vs. time plots for the reaction of cyano-Gilman reagent **1a** with **2** at $-70\text{ }^{\circ}\text{C}$: **1a** (\blacklozenge), **2** (\blacktriangle), **4a⁺** (\bullet), **6/7** (\blacksquare) and **1a + 4a⁺** (\circ). The theoretical curves for **4a⁺** and **6/7** assume no oscillation.

increases, as it is released from a π -complex, which is formed very rapidly upon injection.

Free **1a** (Fig. 1, \blacklozenge) is not observed until 45 s after injection of **2**. Its concentration then increases to a broad maximum at 145 s, whereupon it decreases until it disappears at 400 s. The concentration of free **1b** (Fig. 2, \blacklozenge) also increases to a broad maximum at *ca.* 150 s, but then it decreases to a low, essentially constant level.

The cyanocuprate coproduct, $\text{MeCu}(\text{CN})\text{Li}$ **4a**, is unreactive towards **2** under our conditions; however, it is involved in chemical exchange with **1a** (*cf.* **4a⁺**, Fig. 1, \bullet , *vide infra*). Initially low, the concentration of Ashby's cuprate, $\text{Me}_3\text{Cu}_2\text{Li}$ **5**,¹¹ (Fig. 2, \bullet) increases to a relatively high level during the first 2 s. It then exhibits complex behavior as it decays, owing to the reaction of **5** with **2**.

The concentration of enolates (\blacksquare) from **1a** or **1b** increases to a local maximum, decreases to a local minimum and then increases more or less monotonically. In the reaction with **1a**, we cannot differentiate **6** and **7** (*i.e.*, **6/7**), owing to rapid chemical exchange of methyl groups.⁴ With **1a** or **1b** there is one chemical shift for the enolate vinyl H (4.05 ppm).

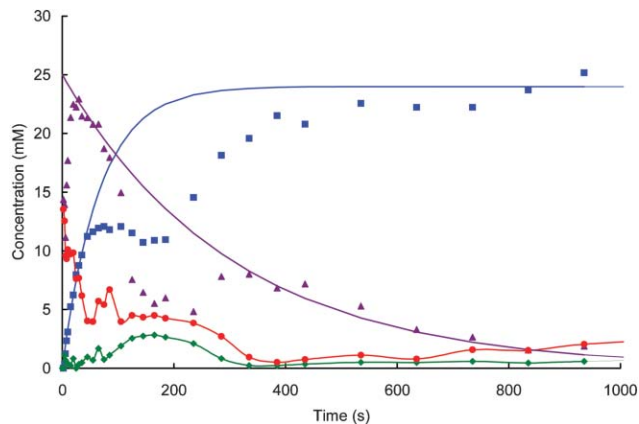


Fig. 2 Concentration vs. time plots for the reaction of iodo-Gilman reagent **1b** with **2** at $-70\text{ }^{\circ}\text{C}$: **1b** (\blacklozenge), **2** (\blacktriangle), **5** (\bullet) and **6/7** (\blacksquare). The theoretical curves for **2** and **6/7** assume no oscillation.

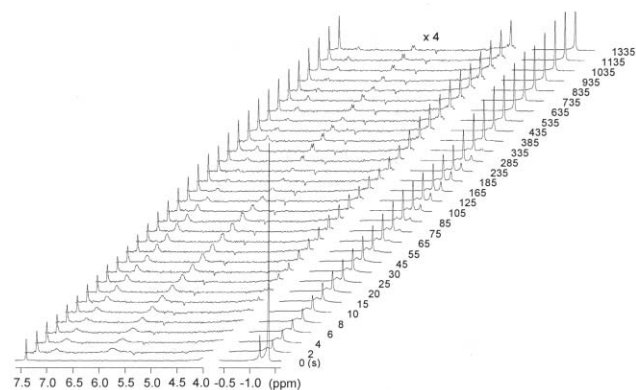


Fig. 3 Stacked plots of ^1H NMR spectra for the addition of **2** to **1a** at $-70\text{ }^{\circ}\text{C}$. The first spectrum is for the cuprate solution before injection.

The bottom spectrum in Fig. 3 was measured for the initial solution of **1a** (-1.34 ppm) immediately before injection of **2**. It shows the presence of a small amount of **4a** (-1.27 ppm), the intermediate in the preparation of **1a** from MeLi and CuCN , which ensures that free MeLi was not present. In the case of **1b** (-1.31 ppm), there was a small amount of **5** (Fig. 4, -0.22 and -1.17 ppm),¹¹ which fulfills the same role. After injection of **2**, substantial amounts of these species are formed (*vide supra*).

The vinyl peaks for π -complexes **3** and **3-LiCN** are coalesced pairwise (H_{α} , 3.8 ppm; H_{β} , 3.2 ppm) by chemical exchange, as are those for **3** and **3-LiI** (H_{α} , 3.7 ppm; H_{β} , 3.2 ppm).⁴ They are very broad and cannot be integrated accurately; therefore, they were omitted from Figs. 3 and 4, as were minor vinyl peaks, which may be due to enolate π -complexes **8** and **9**.¹²

The broad peak at -1.0 ppm in Fig. 3, assigned to the (exchanging) methyl groups of **3** and **3-LiCN**, decreases with time and disappears at 600 s. The methyl groups of **3** and **3-LiI** (Me_{α} , -1.15 ppm; Me_{β} , -0.16 ppm) exhibit similar behavior. We do not discern oscillations in these species, and none are expected, as they are *de facto* starting materials (*vide infra*).

Initially, 2 equiv. of cuprate were present, and 1 equiv. was consumed during the course of the reaction; therefore, 1 equiv. of it should have been present at the end in some form, either free or involved in complexation and/or chemical exchange. Except for

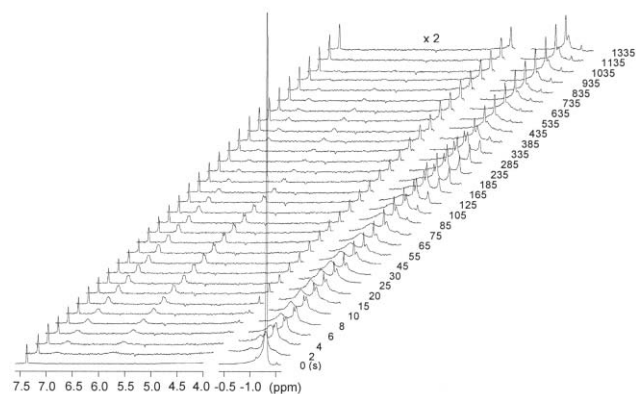


Fig. 4 Stacked plots of ^1H NMR spectra for the addition of **2** to **1b** at $-70\text{ }^{\circ}\text{C}$. The first spectrum is for the cuprate solution before injection.

the interval, 45–400 s, where free **1a** appears, the methyl peak at *ca.* –1.3 ppm must be a composite of the peaks for the methyl groups in **1a** and **4a** and possibly **7** (hence **4a⁺**). The intensity of this peak exhibits very complex behavior, owing to the interplay between the rates of reaction and chemical exchange. The sum of the concentrations of **1a** and **4a⁺** (○ = ◆ + ●), which includes all **1a** as well as **4a**, also exhibits complex behavior. With **1a** the reaction mixture is homogenous; however, the reaction with **1b** is complicated by the precipitation of MeCu.

Unlike oscillating electrical or mechanical systems, oscillating chemical systems do not pass through their equilibrium states. Instead, oscillating chemical reactions in homogeneous media switch between mechanistic pathways on their way to equilibrium, where oscillations cease. Noyes noted that one of the pathways generally involves only even-electron species and the other contains at least one odd-electron species.² Our mechanistic proposal (Scheme 1) features switching between polar and electron transfer pathways, both of which have substantial support in the literature.^{8,13–15}

The rapid formation of *de facto* starting material **3**·LiX from **1** and activated substrate **2**·LiX^{13–15} provides the *sine qua non* for an oscillating reaction: *a system far from equilibrium*.^{1,2} In addition to dissociation (*k*₁) to the original reactants, **3**·LiX can dissociate (*k*₂) to salt-free π-complex **3**,⁴ or it can rearrange (*k*₃) to Cu^{III} intermediate **10**,^{15,16} which undergoes reductive elimination (*k*₆) to **8**. Dissociation (*k*₈) of **8** affords lithium enolate **6** and cuprate coproduct **4**, which may react (*k*₉) to afford copper enolate **7**, an *O*-heterocuprate, which is expected to be stable under our conditions.¹⁷ Enolate π-complex **8** is included between **6** and **10** for stereoelectronic reasons.¹⁸ In all cases known to date *k*_{–6} is vanishingly small, so that this step is essentially irreversible. Generally speaking, products do not oscillate,^{1,2} so that the oscillations in the total concentration of **6/7** are attributed to oscillations in **6**, which is an intermediate. Both enolates would be intermediates were there a subsequent aggregation step.⁷

The second pathway involves electron transfer (ET) from Cu^I reagent **1** to activated substrate **2**·LiX (*k*₄) to give radical anion **11** and a Cu^{II} species,¹⁵ which combine in a solvent cage (*k*₅) to again arrive at common intermediate **10**. The ET mechanism for organocuprate conjugate addition was championed by House,¹⁵ but fell out of favor when π-complexes were discovered,^{13,14} essentially because of Ockham's razor.¹⁹ Our results suggest that the ET hypothesis should be revisited.

The precise nature of oscillatory behavior observed in chemical systems is determined by the balance between positive and negative feedback. The penultimate step in Scheme 1 (*k*₉) produces a net 1 equiv. of LiX, and the last step (*k*₁₀) produces 2 equiv. They are responsible for the positive feedback, as LiX activates **2** (**2** + LiX → **2**·LiX).²⁰ The rate-limiting step in the first pathway is **3**·LiX → **10**, which is first-order, while in the second pathway it is **1** + **2**·LiX → {caged intermediates}, which is second-order. Thus, an increase in the concentration of LiX will tend to favor the latter pathway.

Initially, negative feedback is provided by *k*₂. As the reaction proceeds and coproduct **4** is formed, additional negative feedback may be provided by its reaction (*k*₁₀) with starting cuprate **1** to give a less reactive cuprate, *e.g.*, **5**.¹¹ This aspect of our scheme is similar

to the 'coproduct autocontrol' in the Oregonator model.¹ Since we are operating in a closed system, another source of negative feedback is exhaustion of substrate (limited explodator model).¹ In the case of **1b**, MeCu precipitates from solution, and this system may have characteristics in common with the phase nucleation oscillators.¹

As has often been the case in the history of oscillating reactions, our concentrations of **1** and **2**, which were chosen to optimize the NMR experiment—without any expectation of seeing oscillations, may have serendipitously placed the system in a region of instability. Krause and coworkers followed the kinetics of more concentrated solutions of **1b** and α,β-unsaturated carbonyl compounds by using classical sample-and-quit techniques, and they did not report oscillations.²¹

Chemists have just begun the task of “decoding the ‘black box’ reactivity that is organocuprate conjugate addition”.⁸ We believe that RI-NMR is the key to breaking the code, as it has revealed hitherto unsuspected behavior in this textbook reaction.

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Michael D. Murphy,^a Craig A. Ogle*^a and Steven H. Bertz*^b

^aDepartment of Chemistry, University of North Carolina–Charlotte, Charlotte, NC 28223, USA. E-mail: cogle@email.uncc.edu

^bComplexity Study Center, Mendham, NJ 07945, USA.

E-mail: sbertz@complexitystudycenter.org

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