

Reply to “Comment on ‘Molecules, the Ultimate Nanomotor: Linking Chemical Reaction Intermediates to their Molecular Diffusivity’”

Tian Huang, Bo Li, Huan Wang, and Steve Granick*



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Several studies by our group suggest enhanced mobility of certain molecules during some (not all) chemical reactions. This is likely the result of multiple factors including possibly that the chemical reaction dynamically changes the hydration or solvation layer. Beves, Fischer, and co-workers challenge this view with arguments that the NMR methods we used to detect molecular diffusion are faulty. Here, using the shuffled magnetic field gradient sequence method of diffusion NMR recommended by Beves, Fischer, and co-workers, and considering the CuAAC click reaction that they criticize specifically, we provide new data and analysis that validates our earlier conclusions. Analysis of NMR spectra and of a survey of the literature validates that our study detected chemical reaction intermediates (not the H–D exchange proposed by Beves, Fischer, and co-workers). We endeavor to reconcile opposing arguments of this debate.

Inconsistent interpretation of the same data is a source of confusion in this debate. Concentration changes during the time to acquire a datum would bias the analysis. The method of shuffled magnetic field gradient sequence can be used to minimize such bias.¹ In this Response to critique² of our work, we repeated the earlier measurements using the shuffled gradient protocol and confirm validity of the earlier conclusions.

Our original study of the CuAAC and other chemical reactions made the quasi steady-state hypothesis that such changes are small.³ Soon after, the Beves and Fischer laboratories jointly published that the effects we reported disappeared upon using shuffled gradients,⁴ which was a puzzle because we could not reproduce their data.⁵ This mystery was solved when, having the opportunity to scrutinize their raw data,⁶ we could report that the Beves and Fischer laboratories had published only a portion of the fuller data sets that they deposited online.⁷ The Beves data set⁶ showed the same trends regardless of whether magnetic field gradients were made in ascending, descending, or shuffled order though the Beves–Fischer publication stated otherwise. We also reported inconsistency between data sets from each of the two laboratories, though the publication stated that they agreed.⁷ Data supporting resolution of this apparent disagreement for

the alkyne reagent are summarized in Figure 1. We mention this history because the actual data—when one inspects it closely—show less disagreement than has been stated.

It is most direct to consider the azide reactant which, unlike the alkyne reactant, enters the reaction cycle at just one step. It is now recognized that diffusion NMR spectra of the alkyne reagent include contributions from multiple intermediates of the chemical reaction; on this point, different laboratories agree.^{8–10} Our critics called attention especially to Figure 2E of the paper they challenge, so we redid this experiment using shuffled gradients, as plotted in Figure 2. The findings confirm that diffusion coefficient D_{azide} transiently rises and then falls. Having employed mismatched stoichiometric ratios and lower reactant concentrations than in the original study,³ D_{azide} starts and ends at the same level, so one need not be concerned about the arguments raised recently by Golestani and co-workers¹⁰ regarding what should be the reference point from which to assess the presence or absence of enhanced diffusion, which we challenged¹¹ and Golestani and co-workers defended.¹² In Figure 2, this repetition of our original experiments shows numbers quantitatively somewhat less enhanced than we previously reported, but the qualitative pattern is the same.

The azide diffusion coefficient reported by Golestani and co-workers at matched stoichiometry diminishes during the click reaction,¹⁰ as we had reported. It is natural to suspect thermal effects (though Beves and co-workers report no reaction-induced temperature increase⁹), but if this were the case, other chemical species should behave similarly yet do not show this decreasing trend of the diffusion coefficient. Golestani and co-workers interpret it as an uninteresting outcome of peak overlap,¹² but this is implausible because their

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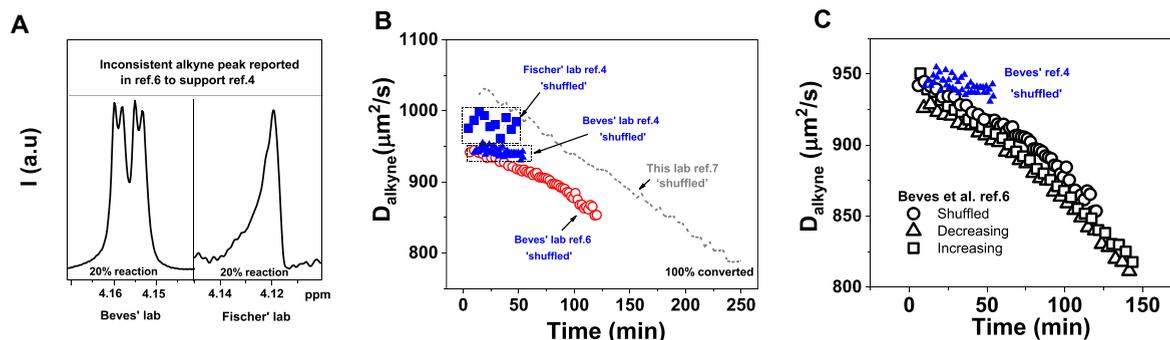


Figure 1. Analysis of the asserted inability to reproduce our findings, ref 4, cited in this Comment to support the authors' arguments. (A) Raw data using diffusion NMR to analyze the CuAAC reaction, deposited online,⁶ shows that the Beves and Fischer laboratories measured inconsistent NMR peaks of the methylene alkyne proton under the same reaction conditions. (B) Time-dependent D_{alkyne} evaluated from the raw data deposited online shows that the published measurements showing constant values regardless of reaction using shuffled gradients (ref 4) are inconsistent with data the Beves' lab measured at later reaction times, and this information was not included in ref 4. (C) Time-dependent D_{alkyne} evaluated from the raw data deposited online,⁶ shows the same trend for shuffled (circles), increasing (squares), and decreasing (triangles) magnetic field gradients, which is inconsistent with statements in ref 4. These data are compiled from reading data from ref 4 and by adapting some data from ref 7.

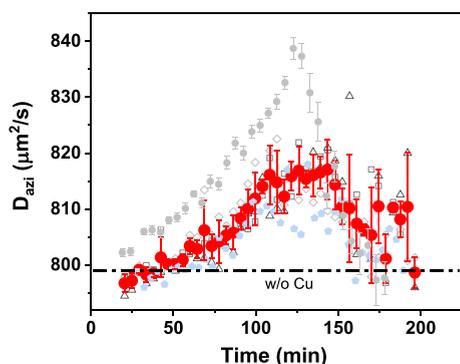


Figure 2. Four new experiments showing the time-dependent D_{azide} for the CuAAC reaction, all obtained using shuffled gradients of the magnetic field in a 600 MHz FT-NMR (Agilent) with pulse sequence, DgcsteSL_cc (gradient compensated stimulated echo with spin-lock and convection compensation). Concentrations of the chemical species are the same as in the subject of this Comment, ref 8 (alkyne/azide = 75:90 mM). Red circles show the average of three independent measurements on different days (square, rhombus, triangle) with measurement parameters pulse width = 11.5 μs , relaxation delay time (D_1) = 7 s, number of scans (NS) = 4, gradient duration (δ) = 1.5 ms, diffusion time (Δ) = 50 ms, and shuffled gradient order 3, 6, 1, 5, 4, 2, 7 (1–7 denote monotonically increasing order magnitude). A fourth independent experiment (pentagons): D_1 = 8.5 s, NS = 2, and shuffled gradient order 1, 10, 4, 2, 9, 8, 11, 3, 7, 6, 5 (1–11 denote monotonically increasing magnitude). Integration range 0.01 ppm was used to obtain the peak intensity. Homebuilt code written in IDL (interactive data language) was used for data analysis. Data in ref 8 are shown for comparison (gray circles).

data were acquired using a high-resolution 800 MHz NMR instrument. It is more plausibly consistent with our findings.

There remains the objection that they present as baseline "reference" that azide diffusion is slower during chemical reaction than in the reaction mixture lacking catalyst,¹² but this is inconsistent with the following technical analysis. Their reported diffusion coefficient of alkyne alone ($\sim 1110 \mu\text{m}^2/\text{s}$), alkyne in Cu(II)-free reaction mixture ($\sim 1020 \mu\text{m}^2/\text{s}$), and azide alone ($\sim 840 \mu\text{m}^2/\text{s}$) (read from ref 12) all are close to the numbers that we measure: alkyne alone ($\sim 1080 \mu\text{m}^2/\text{s}$), alkyne in Cu(II)-free reaction mixture ($\sim 1000 \mu\text{m}^2/\text{s}$), azide

alone ($\sim 820 \mu\text{m}^2/\text{s}$). Their measurements for these conditions are consistently larger than ours by $\approx 2\%$, suggesting some difference in instrument calibration, but when it comes to "reference" azide diffusion in the reaction mixture lacking catalyst, their $\sim 790 \mu\text{m}^2/\text{s}$ (read from ref 12) is faster than our $\sim 750 \mu\text{m}^2/\text{s}$ by $\sim 5.5\%$. If this number had followed the same apparent instrumental discrepancy (2%) as for the other peaks, it would have been $\sim 760 \mu\text{m}^2/\text{s}$, i.e., slower than what they report during chemical reaction and accordingly plausibly consistent with what we report. It is hard to explore this inconsistency because Golestanian and co-workers¹² present a horizontal line in a graph (not data) as evidence. It is striking that only for this "reference", not for the other peaks that can be compared, this substantial discrepancy is revealed.

Another critique² is that lengthy longitudinal relaxation constant T_1 of water renders our data faulty. Elsewhere, Beves, Fischer, and co-workers repeated the CuAAC reaction in the presence of gadolinium ions to speed up T_1 . Finding no diffusion enhancement,⁹ they cite this as evidence the effect does not exist, but elsewhere, we articulated faults in their reasoning.¹¹ An extensive older report shows that gadolinium ions are unsuitable for diffusion NMR because their large magnetic moment and electric charge cause them to interact strongly with protons by continual binding–unbinding to eight chelated ligand sites and a ninth coordination site on the core Gd^{3+} ion itself.^{13,14} We interpret intensity rise of the HDO signal to reflect the presence of water coordination sites offered by complexation of bimetallic Cu–Gd–DTPA^{15,16} to induce intensity loss of water from the blind sphere effect.¹⁷

Analysis of the water peak in our original diffusion NMR publication³ was, in hindsight, deficient in not recognizing the need to disentangle the respective contributions of water in potentially a large variety of water microenvironments encountered during the CuAAC reaction. In order to determine the existence (or not) of the enhanced diffusion effect, it is more promising to focus on those molecular species that actually react chemically.

Beves, Fisher, and co-workers, in their attempt to reinterpret our measurements of chemical intermediates, propose a significant contribution from hydrogen–deuterium isotope exchange on alkyne. This is not supported by inspecting the $^4J_{\text{HH}}$ coupling loss of the propargylic ^1H resonance. This one

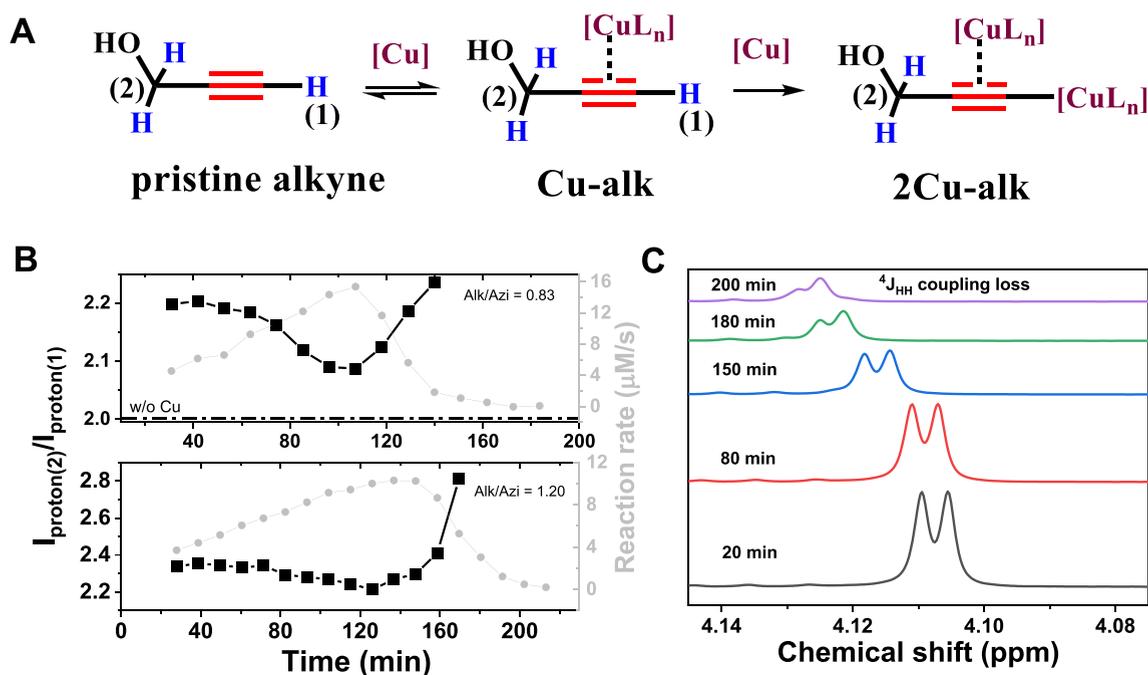


Figure 3. Analysis of reactions leading to the 2Cu-alk intermediate in the CuAAC reaction. (A) Reaction scheme showing terminal and internal protons (1 and 2, respectively). The stoichiometric ratio of Cu to alkyne is less than 2 when the same metal complex coordinates to multiple alkyne molecules. (B) Peak intensity ratio of terminal and internal protons (left ordinate) and the reaction rate (right ordinate) plotted against reaction time for alkyne/azide = 75:90 mM (top panel with data adapted from ref 8) and alkyne/azide = 90:75 mM (bottom panel, new data). (C) Five representation spectra illustrating the progressively larger $^4J_{\text{HH}}$ coupling loss of proton 2 during the reaction in the bottom of panel B, which is inconsistent with the isotope exchange hypothesis in ref 2.

can be seen by inspecting the progression from one terminal proton (pristine alkyne) to the absence of terminal proton (2Cu-alk complex) in the scheme summarized in Figure 3A. Regardless of whether azide or alkyne is in excess, the intensity ratio of the two protons sees a minimum near the point of maximum reaction rate (Figure 3B) and, in both cases, increases toward the end of the reaction, reflecting increased abundance of 2Cu-alk.

We now address the argument about the intensity ratio of the interior and terminal protons of the alkyne reagent, which in pristine alkyne is identically 2. In the reaction intermediate 2Cu-alk, the terminal alkyne proton is replaced by Cu(I). The coordination of Cu and alkyne in the acetylide is fast and experiences a rapid degenerate rearrangement,¹⁸ so it is normal that only one set of NMR signals was observed, but the hydrogen intensity ratio exceeds 2, reflecting the presence of the 2Cu-alk intermediate. Regarding the concentration of 2Cu-alk that we calculated, our paper had explained that because other ligands of 2Cu-alk can be water, ascorbate, and other alkyne molecules,⁸ the ratio of Cu and alkyne is not identically 2 but can also be 1 or <1.¹⁹ Therefore, Beves, Fischer, and co-workers are incorrect when they assert (claiming that our data are internally inconsistent) that according to mass conservation the maximum achievable concentration of 2Cu-alk is $10.3 \text{ mM}/2 = 5.15 \text{ mM}$. In fact, studies in the organometallic chemistry literature¹⁹ show coordination of the same metal complex to multiple alkyne molecules, resulting in a stoichiometric ratio between Cu and alkyne of <2.

As one sees in Figure 3C, the $^4J_{\text{HH}}$ coupling loss is most evident near the end of the reaction, reflecting accumulation of the 2Cu-alk complex. During reaction, the terminal proton peak shows significant chemical shift to low field, as others also reported,^{8,10} resulting from reduced electron density by CuL_n

coordination, which induces deshielding and does not support the proposed alternative explanation of H–D exchange. Regarding the cited paper about H–D exchange of Cu-acetylide in the click reaction, it is not relevant because the system in that study differs so much from the system we studied. In that study, the PPh_3 and OAc basic counterions of the Cu(I) salt were capable of furnishing H–D exchange²⁰ because the terminal proton of alkyne is unstable in the basic conditions at which that reaction was performed. However, our reaction was in an acidic environment in the presence of azidoacetic acid.

Beves, Fischer, and co-workers also challenge our data using a simulation. Predicting a result that is inconsistent with the actual experiment using shuffled gradients (Figure 2), they reinterpret data we had obtained using ascending magnetic field gradients⁸ and conclude that their simulation suggests no diffusion enhancement. The reasoning behind this simulation would have held up if it had been the case that the enhanced diffusion phenomenon is in one-to-one correspondence with concentration changes of the azide reactant. The discrepancy supports our own reasoning. In the paper to which these authors object, we argued that the diffusion of reactants may be connected to the hydrodynamic consequences of how the chemical reactions transiently modify the solvation shells of reacting molecules—evidently, this must include not only the azide reactant but also all other chemical species.⁸ The simulation of Beves, Fischer, and co-workers tends to validate our approach to the problem.

The chemical reaction intermediates after formation of the 2Cu-alk complex, summarized in Figure 4A, are also interesting to consider. Using the shuffled magnetic field approach urged by Beves, Fischer, and co-workers, we repeated our earlier inference of diffusivity of the 2Cu-alk complex and find

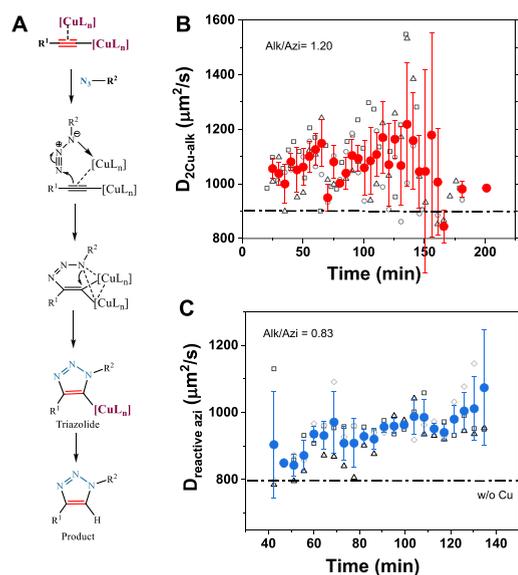


Figure 4. Analysis of reactions subsequent to the 2Cu-alk intermediate in the CuAAC reaction. All of the diffusion NMR measurements use shuffled gradients. (A) Reaction scheme showing addition of the azide reactant as the first indicated step. (B) Inferred diffusion coefficient of the 2Cu-alk intermediate is plotted against reaction time in the situation of alkyne excess (alkyne/azide = 90:75 mM), using arguments described in ref 8 to infer $D_{2\text{Cu-alk}}$. Filled circles are the average of three independent experiments with the following parameters: pulse width = 11.5 μs , $\Delta = 50$ ms, squares: $D_1 = 7$ s, NS = 4, $\delta = 1.5$ ms, convection suppression, and shuffled gradient order 3, 6, 1, 5, 4, 2, 7 (1–7 denote monotonically increasing magnitude). Open circles: number of gradients = 16, $D_1 = 15$ s, NS = 1, $\delta = 2.0$ ms, convection suppression, and shuffled gradient order 1, 13, 11, 8, 15, 12, 7, 6, 10, 14, 3, 2, 5, 4, 9, 16 (1–16 represent monotonically increasing magnitude). Triangles: $D_1 = 15$ s, NS = 1, $\delta = 1.5$ ms, convection suppression, and shuffled gradient order 1, 13, 11, 8, 15, 12, 7, 6, 10, 14, 3, 2, 5, 4, 9, 16 (1–16 represent monotonically increasing magnitude). (C) Inferred diffusion coefficient of reactive azide inferred from the equation described in the text. Filled circles: average from three independent experiments. Measurement parameters are the same as those in Figure 2.

agreement (Figure 4B). Regarding the azide reagent, it is natural to consider the analogous calculation. The average D_{azide} has contributions from some azide that is in the process of reacting, and other unreacted azide that has not yet participated in the chemical reaction. Expressed as an equation, the argument can be stated as $D_{\text{measured}} = D_{\text{unreacted}} \times a + D_{\text{reactive}} \times (1 - a)$, in which the respective D contributions are weighted by their relative abundance a and $(1 - a)$ to the total azide signal intensity. This allows D_{reactive} to be deduced from measurements of the first two with the zero-order assumption that diffusion coefficient of unreacted molecules ($D_{\text{unreacted}}$) is unaffected during the chemical reaction. Using the same calibration method used in ref 8, we identified $D_{\text{unreacted}}$ as the measured azide diffusion coefficient under the same reaction concentrations as those for subsequent reaction, except that Cu^{2+} catalyst was removed from the mixture.⁸ Implementing this attempt to separate the different contributions, we obtain the findings in Figure 4C. Here, D_{reactive} systematically exceeds $D_{\text{unreacted}}$, but we are unable to assess whether the tendency to increase toward the end of reaction exceeds the error bars. A possible explanation is that more azide molecules are under reaction toward the end, but it might be just uncertainty of this

calculation. With the acknowledged limitation that this argument assumes $D_{\text{unreacted}}$ is unaffected by reaction, the calculation predicts diffusion increase on the order of 10–20%, roughly the same fractional increase as that for $D_{2\text{Cu-alk}}$. Note that the time scales of change in Figure 4B,C are different because they refer in the first case to alkyne excess and in the second case to azide excess.

Others have objected that our measurements are inconsistent with theory.¹⁰ Survey of the literature shows that fundamental deviations from the Stokes–Einstein equation were discovered long ago^{21–23} (they too were controversial at the time). We have proposed avenues of possible interpretation of our experiments.⁸ Independent theoretical models by others have begun to appear.^{24–26} All of these models go beyond the assumptions by authors of this Comment that no time-dependent changes can be anticipated.

In summary, having carefully considered the specific points raised in this Comment, as well as others in recent literature, and having performed new experiments to test the validity of the criticisms, we stand by our original conclusions and thank the authors for their interest in our work.

AUTHOR INFORMATION

Corresponding Author

Steve Granick – Center for Soft and Living Matter, Institute for Basic Science (IBS), Ulsan 44919, South Korea; Departments of Chemistry and Physics, Ulsan National Institute of Science and Technology (UNIST), Ulsan 44919, South Korea; orcid.org/0000-0003-4775-2202; Email: sgranick@gmail.com

Authors

Tian Huang – Center for Soft and Living Matter, Institute for Basic Science (IBS), Ulsan 44919, South Korea
Bo Li – Center for Soft and Living Matter, Institute for Basic Science (IBS), Ulsan 44919, South Korea
Huan Wang – College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P.R. China; orcid.org/0000-0002-2542-936X

Complete contact information is available at:

<https://pubs.acs.org/10.1021/acsnano.2c04698>

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