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# Response to Comment on “Boosted molecular mobility during common chemical reactions”

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Günther *et al.* report that their control experiment using randomized magnetic field gradient sequences disagreed with findings we had reported using linear gradients. However, we show that measurements in our laboratory are consistent using both methods.

In a recent report (1), we used pulsed-field gradient nuclear magnetic resonance (NMR) to analyze the molecular mobility of reactants and nearby solvent. We concluded that mobility during several common chemical reactions is more rapid than Brownian diffusion when the free energy release rate exceeds a threshold. This is in pleasing agreement with a master curve that reveals similar boosted mobility of catalytic enzymes, reconciling previous conflicting data in the literature (2). Boosted mobility was confirmed using an independent microfluidic gradient method. The Comment by Günther *et al.* (3) describes their concerns regarding our NMR measurements.

Our original report predicated its NMR measurements on using the standard method—monotonically increasing the gradient amplitude of the magnetic field—thereby creating the hypothetical possibility that intensity changes during the reaction from reactant consumption result in a biased apparent change of the diffusion coefficient. In Fig. 1 we compare findings using randomized gradients recommended by Günther *et al.* (3) with those in our original report (1). The figure also shows findings using linearly decreasing gradients. All three methods are consistent.

This is anticipated by the design of our experiment. We had selected chemical reaction conditions with rates sufficiently slow to permit 3 to 5 min of signal averaging per data point and therefore to check the validity of the steady-state assumption that underlies the data analysis (1). Concentration changes were not confounding, as our experiments were performed on a time scale during which concentrations varied only negligibly. Figure 1 of Günther *et al.*, based on simulated data, is therefore not germane because it shows the effect of changing the observable by up to

80% during the experimental time window, contrary to the situation in our experiments.

Figure 2 of Günther *et al.* notably contains no information about chemical reaction rates in their experiment. In our experiments, the reaction times were 100 min or longer [figure 1D and figure S8 of (1)], longer than the 15 to 20 min in these data by a factor of at least 5. The time scales are inconsistent. Respectfully, we consider it doubtful that the reaction conditions were the same as ours. We found that the boosted diffusion phenomenon could only be observed when the threshold energy release rate for the given chemical reaction was exceeded.

Günther *et al.* object that changes in spin-lattice relaxation  $T_1$  during the pulse sequence and diffusion delay could lead to a change of signal intensity that would be misinterpreted as a modified apparent diffusion coefficient. Yet we used relaxation delays long enough for magnetization to return to equilibrium, as described in our experimental design (1). Our experiments [described in table S2 of (1)], with variable diffusion delays giving the same diffusion coefficient, argued that changes in signal intensity during spin-lattice relaxation did not cause mistakes. These considerations probably explain why, when we repeated the experiments using randomized field gradients, we found consistency.

Günther *et al.* find our data strange because in some instances different moieties on the same molecule display different diffusion coefficients. Yet this is well accepted for the case where protons exchange rapidly with deuterons in solvent, such as peak 9 in figure S2A of (1). The case of chemical reactions, where different intermediates survive for different times during the reaction cycle, was discussed in

“Diffusion of reaction intermediates” in the supplementary materials of (1). We confirmed this conclusion using randomized magnetic field gradients.

The above factual evidence and reasoning give additional support to this laboratory’s conclusions regarding boosted diffusion during common chemical reactions (1, 2).

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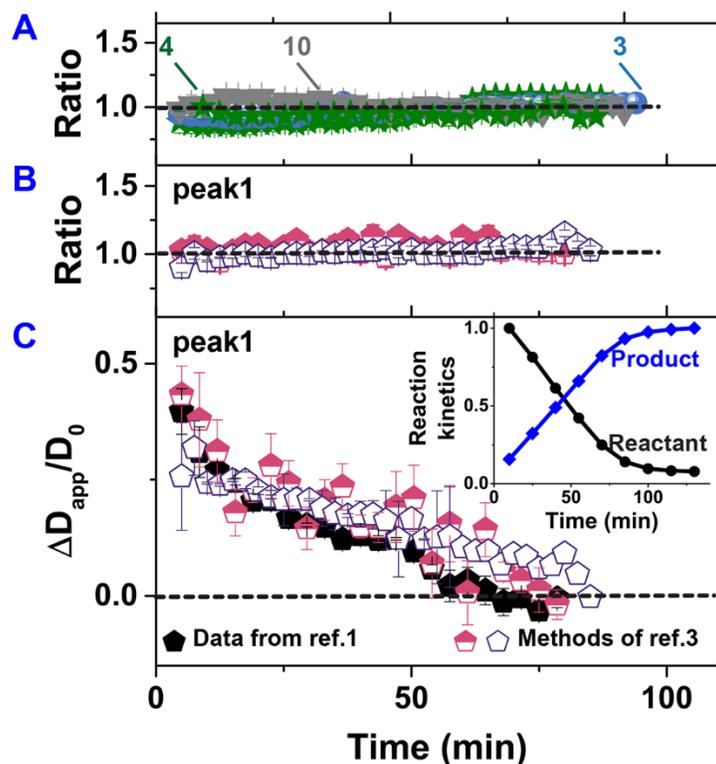
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**Fig. 1. Increased diffusion during click chemical reaction compared using randomized, linearly decreasing, and linearly increasing magnetic field gradients.** Linearly increasing gradients were used in our original report (1). Günther *et al.* recommend randomized gradients instead (3). (A) Ratio of diffusion coefficients measured using randomized gradients to those measured using linearly increasing gradients for the chemical moieties 3, 4, and 10 identified below and in the original report, plotted against reaction time. Peak 4 (stars) = alkyne at 4.2 ppm; peak 3 (circles) = azide at 3.85 ppm; peak 10 (triangles) = ascorbate at 3.98 ppm. Dashed line indicates ratio = 1. (B) Ratio of diffusion coefficients measured using randomized gradients (half-filled pentagons) and linearly decreasing gradients (open pentagons) to those measured using linearly increasing gradients (filled pentagons), plotted against reaction time. These data are for peak 1 = alkyne at 2.1 ppm. (C) Boosted diffusion of the alkyne reactant plotted against reaction time using randomized (half-filled symbols), linearly decreasing (open symbols), and linearly increasing magnetic field gradients (filled symbols). Inset shows chemical reaction kinetics for the click reaction under these reaction concentrations (1). Measurements were made under the same conditions as in the original report (1) using the 400-MHz FT-NMR (Bruker, AVANCE III HD) in our university. In all cases we used the standard stimulated echo bipolar gradient pulse pair with one coil, stebppg1s, with pulse duration  $\delta = 2900 \mu\text{s}$ , diffusion time  $\Delta = 50 \text{ ms}$ , and delay between scans  $D = 3 \text{ s}$ . Randomized pulse sequences were made using 100% nonuniform sampling provided by Bruker software such that relative to the maximum magnetic field gradient of  $45 \text{ G cm}^{-1}$ , the pulse gradient was ramped randomly between 5% and 95% in the order 5%, 35%, 89%, 29%, 17%, 59%, 65%, 23%, 41%, 11%, 53%, 47%, 71%, 77%, 95%, and 83% in 16 steps. Linearly increasing and linearly decreasing gradients were a built-in function of the Bruker software.

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