On maintaining standards in chemistry

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In this work Yang *et al.* [1] claim that an enantioselective Michael addition reaction with a barrier of 16 kcal/mol occurs at the single molecule level in frozen solvent by measuring fluctuations in current flowing across graphene based molecular devices. If true, such methods would provide a leap forward in understanding reaction mechanisms. However such strong conclusions need strong experimental evidence, which, as we detail in this Matters Arising, is lacking in the work of Yang *et al.* [1].

Typically, advances in synthetic chemistry have thrived based on a strong tradition of providing analytical evidence for compounds formed using methods such as nuclear magnetic resonance (NMR), high-performance liquid chromatography (HPLC), high resolution mass spectroscopy (HRMS) as well as structure identification using x-ray techniques. These methods often require macroscopic quantities of the products. This makes such characterizations difficult when molecules are synthesized one at a time. Although there are no techniques available for single molecule NMR analysis yet, there are many other experiments that could have been performed to show proof of synthesis at the single molecule level. Unfortunately, as we show here, in the work of Yang *et al.* [1] the evidence provided is insufficient, often inconsistent, and even misleading, leaving us to conclude that the results appear to be too good to be true.

The Fabrication of the Devices Leaves Many Unknowns
The experiments described in the work of Yang *et al.* are based on the fabrication of graphene electrodes separated by a small distance, which should allow bridging by a single molecule. The electron-beam fabrication methods are not accurate enough to produce the gap distance controllably, and this problem is addressed by making many, i.c. 210, of such gaps in parallel, and relying on the inevitable variation in distance to randomly produce gaps of different width. Immersion of the devices in a solution containing the molecules is claimed to produce, in relatively high yield, bridges formed by single molecules. Although Yang *et*

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al. claim that the graphene electrodes are terminated by carboxyl groups by the fabrication procedure, this is not obvious, and has not been demonstrated experimentally. The molecular anchoring groups are designed to bind to such carboxyl groups. No independent verification of the molecular bridging geometry is provided, other than what can be concluded from resistance measurements. This should a warning to be careful with conclusions. For example, the six phenyl groups of the molecule are likely to bind by pi-stacking on top of the graphene, leaving room for many different binding configurations. None of the experiments described exclude such alternative binding.

The Magnitude of Measured Current: Eight Orders of Magnitude Missing

When synthesis is claimed to occur one molecule at a time, it may not be possible to characterize products using NMR, HPLC or HRMS. It is, however, possible to measure a characteristic single-molecule conductance (or current) and show that the same is observed with the *ex-situ* synthesized and characterized product. This minimal level of verification, which is well documented in the literature [2, 3, 4], has not been followed in the work of Yang *et al.* Instead, the authors choose to confirm that the measured currents can be attributed to single-molecule junctions using density functional theory (DFT) based calculations. What is odd about their published results (comparing Figure 2b and Supplementary Fig. 15) is that the calculated currents, following the Landauer-Buttiker formalism (Eq. 1), are $10^7 - 10^8$ times smaller than those measured in the experiment.

$$I = \frac{2e}{h} \int_{-\infty}^{\infty} dE \ T(E)(f_L(E - eV/2) - f_R(E + eV/2)) \simeq \frac{2e^2 V}{h} T_{avg}(E_F); \qquad (1)$$

Specifically, the average transmission ($T_{avg}(E_F)$) around the Fermi energy in Supplementary Fig. 15 is $\sim 10^{-10}$. Using known values for the charge of an electron (e), Planck's constant (h), and voltage $V = 300$ mV, and assuming zero temperature (to set the left and right Fermi-Dirac distribution functions (f_L, f_R) to 1 within the bias window and 0 outside), we obtain a theoretical current of $\sim 2.6 \times 10^{-15}$ A, much smaller than the measured current of 2.5×10^{-7} A in Figure 2A. Note that the calculated current reported in Figure 2b, must have been obtained from the DFT results by 'correcting' for a factor 10^8, without informing the reader of this dubious procedure.

Although DFT calculations have well-known errors that are inherent to the method, these errors result in the theory *overestimating* currents by one or two orders of magnitude [5, 6, 7, 8]. An *underestimation*, and especially by more than eight orders of magnitude, cannot be attributed simply to DFT-errors. Thus, the currents in the 50-300 nA range at a bias ~ 0.3 V measured across a hexa-phenyl derivative cannot be attributed to that of a single-molecule junction.

We conclude that the authors never formed a single-molecule junction with the hexaphenyl derivative bound to graphene electrodes as such a device should have, based on their calculations, currents in the femto-Ampere range, which would be hard to detect. The device fabrication methods as detailed in SI Section 2 suggest that it is seems to indicate that there are many devices in parallel bridging two graphene electrodes. This is especially clear in Supplementary Fig. 2. It is possible that they are measuring many molecular junctions in parallel, in which case the main claim of observing reaction chemistry at the single molecule level cannot be correct. Alternatively, the bridges could be formed by pi-stacking interaction on top of the graphene basal plane by only one of the arms of the molecule. It is even conceivable that

graphene flakes re-arrange during wetting by the solvent, such that they bridge one or more of the 210 parallel bridges.

IETS Spectroscopy: Inconsistent with Experimental Resolution

The second piece of evidence for the bridging of the graphene electrodes by this particular single molecule is given by the recorded Inelastic Electron Tunneling Spectra (IETS), shown in Supplementary Fig. 8. The information in the caption of this figure is not sufficiently detailed to establish the experimental protocols. Typically, it is is very hard to obtain reproducible spectra for IETS, and the recording of IETS spectra requires long averaging times. Seeing that the bias voltage is ramped up to voltages above 0.4 V, the switching of the molecule between the various states should prohibit the recording of stable spectra.

However, the key factor is the modulation voltage used for recording the spectra; this is given as $V_{\mathrm{mod}} = 21.2$ mV. This amplitude limits the resolution of the spectral peaks to $1.2\sqrt{2}V_{\mathrm{mod}} = 36$ mV (FWHM) [9]. The two most prominent peaks in Supplementary Fig. 8a have a width of only 5 mV. The conclusion must be that the signals shown in the figures are spurious signals, and they cannot be interpreted as IETS signals.

Chemical Reactions in a Frozen Solvent?

Solvent based reaction chemistry is typically done at temperatures for which the solvent is in a liquid state, and the available thermal energy enables the reactants to come in close proximity, facilitating synthesis. In the work of Yang *et al.* [1] the authors claim to have carried out a Michael addition reaction at temperatures below 120 K in ethanol, which freezes at 160 K. Although for rare reactions using water as the medium for synthesis, reactant concentration can increase below 273 K, as ice formation expels solutes, thereby enabling chemistry [10]. The claim by Yang *et al.* that the Michael addition is possible below 120 K in ethanol, is a exceptional claim. Exceptional claims require exceptional evidence. If the reaction proceeds as claimed one should demonstrate this *ex-situ* and use standard chemical characterization techniques (NMR, HRMS, HPLC) to prove that products are indeed formed. Unfortunately, such analyses were absent in this work questioning whether the reaction occurs under their experimental conditions.

The energetics of this reaction is also problematic. The Michael addition reaction of the 1,3-dicarbonyl compound to maleimide involves breaking a double bond on the maleimide followed by the formation of two single-bonds after a proton transfer from the ethanol solvent. This reaction normally proceeds in the presence of an acid (e.g. trifluoroacetic acid) and a catalyst that ensures a high yield [11, 12]. The reaction barrier for this Michael addition is 16 kcal/mol (~ 0.7 eV), based on the calculations presented by Yang *et al.* (Figure 2c) [1]. The authors claim further that the theoretical reaction barrier is reduced to 2 kcal/mol (0.09 eV) under an electric field of 2.57 V/nm. Given the junction length (~ 3.2 nm, set by the length of the molecule), achieving fields as high as 2.5 V/nm would require bias voltages greater than 8 V across the device, assuming that the voltage drops uniformly across the junction. In most molecular junctions, the voltage drop is primarily at the contacts [8, 13] thus even higher biases would be required to achieve fields as high as 2.5 V/nm at the reaction site. The experimental bias of 300 mV yields a field of 0.2 V/nm, again assuming a uniform voltage drop. At the experimental fields used in this work, the probability of observing the Michael addition within experimental time scales is basically zero.

The Michael addition considered in Yang *et al.* has six different possible products, as illustrated in Figure 1, four of which do not involve a proton transfer from the solvent. In
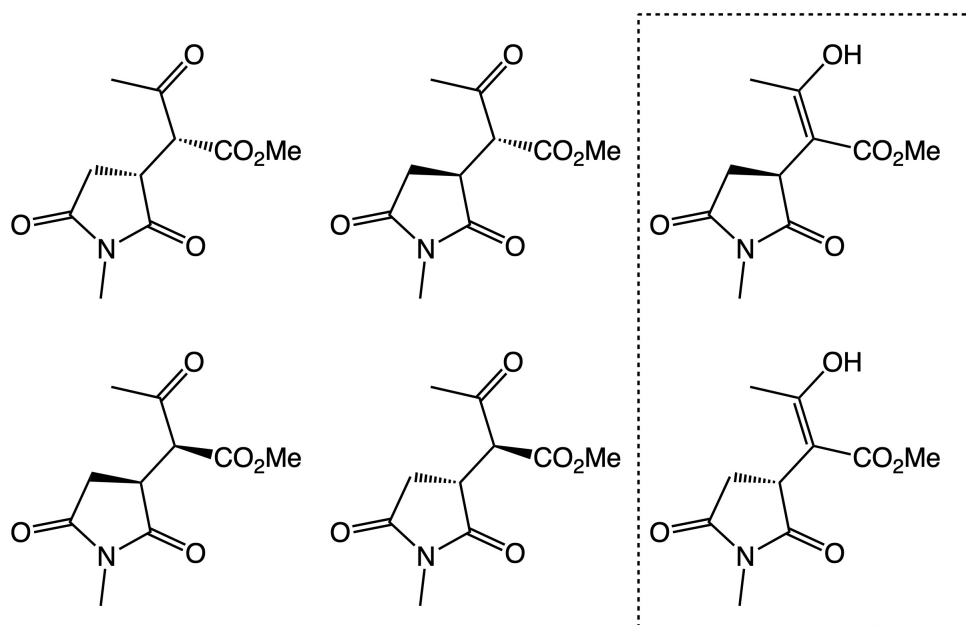
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Figure 1: Six different possible products that can be formed from a Michael addition reaction of 1,3-dicarbonyl compound to maleimide. The box highlights the two considered in the work of Yang *et al.*, which both require a proton transfer.

the work of Yang *et al.*, the authors only consider, without justification, two of these six possible products, the ones that include a proton transfer. However, the synthetic procedures [11, 12] clearly state that enantioselectivity and diastereoselectivity can vary widely depending on conditions and substrate identity. To conclude that only two of the six possible outcomes are possible under any particular experimental conditions (let alone in the frozen solvent under a low external field and without catalysts or acid) requires significant analysis and mechanistic understanding. Again, such supporting evidence is lacking in the work of Yang *et al.*

Realtime Monitoring and Chirality Determination: Misinterpretation of Noise

The primary evidence that the authors use to support the claim of observing the Michael addition reaction in real time is the measurement of fluctuations in the current across their device that has the maleimide reactant tethered to it. The authors assume that the current fluctuations result from the 1,3-dicarbonyl compound binding to the maleimide. Such fluctuations in current as a function of time are widely known as random telegraph noise (RTN) and have been studied and observed for many nanoscale systems, and can be attributed to a slew of physical phenomena [14]. Although RTN signals could result from the proposed reaction taking place within the measurement timescales, seeing RTN does not prove that a chemical reaction is in process. It is much more likely that the RTN results from rearrangements of the atomic scale structure of the device (whatever it is), which can be activated simply by increasing the current (or the voltage bias) across a molecular-scale device.

Control experiments, such as presented in Supplementary Fig. 9, are intended to verify that that the RTN signal is absent in the absence of the reactant. However, this is not a valid control. First, it is a different device. Second, the currents are much lower than those in the experiments shown in Fig. 2. Since RTN is known to be activated by current (and voltage) over

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the junction, a valid control should use the same the device at the same current. The currents in Supplementary Fig. 9, especially for the lower temperatures, are upto a factor of 30 smaller than those shown in Fig. 2. For lower currents RTN is likely to disappear. Note also that the current is different for each temperature in Supplementary Fig. 9, and is set systematically lower for decreasing temperature. RTN will be more prominent at low temperatures, and one would need to limit the current bias in order to avoid the switching from appearing. This raises the suspicion of purposeful data manipulation. The scientific community requires a lot more evidence when claims are made of probing reaction mechanisms in real time.

Finally, we note that the authors claim to determine, in real time, the chirality of the product formed by monitoring the spin polarization of the transmitted electrons through the molecular junction, a method that relies on the Chirality Induced Spin Selectivity (CISS) effect [15]. Although the CISS effect is poorly understood [16], any spin polarization resulting from electron transmission through chiral molecules can only have a component parallel to the current direction. Interestingly, the direction of the magnetic field applied in the experiments of Yang *et al.* as shown in Fig. 1b and as described in the manuscript [17] is orthogonal to the direction of the direction of the current flow. Any effects of the magnetic field on the current measured through their molecular junctions must therefore be unrelated to the CISS effect, and cannot be interpreted in terms of the chiral structure of the molecules that are claimed to be synthesized. While a claim of enantioselective reaction mechanisms that can be observed through real-time monitoring of currents across single molecule devices is effective in drawing attention, supporting evidence for the conclusions are critical to provide a solid foundation for scientific advances.

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[17] As stated in the manuscript on page 975, the authors claim that "The Ni electrode was then magnetized by applying a $\pm$T magnetic field parallel (and anti-parallel) to its axis." This can only be read as referring to the axis of the Ni electrode.