Reply to the Comment on “On the S_N2 reactions modified in vibrational strong coupling experiments: reaction mechanisms and vibrational mode assignments”

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In September 2020, we became aware that a comment[1] on our recent paper[2] had been posted to ChemRxiv. Since our attempts in October 2020 to reach out to the authors to discuss the points they raised did not receive a response as of April 2021, and the comment was not submitted as a formal comment to the original journal either, we here provide a brief reply based on the results that were already reported in our original manuscript. Most importantly, we show that we did not “presumably overlook*”* any data in the supplementary material of their original article, but that our results are actually fully consistent with those data.

The authors of the comment first state that we claimed that the original experiments reached strong coupling with vibrational modes of the solvent. That is a misunderstanding of the discussion in our article. We (intentionally) did not state that strong coupling with the solvent modes was reached – we agree that the experimental data do not support this statement. We only mentioned that higher-order cavity modes were close to resonance with solvent modes in some cases, and that solvent vibrations are “coupled to” the cavity modes. Still, it seemed pertinent to us to point out the possibility that the coupling to the solvent could play a role, due to the following reasons: First, works from the same authors show modifications of chemical reactivity under strong coupling to solvent modes.[3] Second, the distinction between weak and strong coupling is not clear-cut in systems with disorder and broad line shapes, since there is always some hybridization if states are close to resonance and the coupling is sufficiently strong. Accordingly, we are not aware of any data that show the effect on chemical reactivity disappearing “abruptly” as the concentration is decreased and the system goes out of strong coupling (e.g., Fig. 3a in reference 4 starts at concentrations already in the strong coupling regime). Second, while an effect of being on resonance is clearly seen in the experiments, it does not seem to always require exact resonance (e.g., Fig. 3A in reference 5 shows an effect when the cavity is tuned to just above and below 1200 cm^{-1}, neither of which is exactly on resonance with a vibrational mode). Furthermore, since efforts to provide a microscopic understanding of these experiments have not been successful yet,[6–13] we believe it might be useful to look into effects that at first sight seem unlikely to be responsible. Finally, in the experiments reported in reference 4, the reaction rate showed a dependence with the Rabi splitting (Figure 3 in reference 4), but it should be noted that the concentration of the solvent is also varied when the Rabi splitting is changed (as stated in reference 4: “The concentration-dependent experiments were carried out by varying the PTA concentration from 0.87m to 3.37m at a TBAF concentration of 0.36m ([MeOH] was varied to maintain [TBAF])”). We also mention that since the comment was uploaded to ChemRxiv before the final version of our paper was published, we took the opportunity to clarify some statements on this topic in the proof corrections to prevent such misunderstandings.

The authors of the comment further state that we "presumably overlooked" "an unequivocal assignment that was in the supplementary material" of reference 5. We did not overlook this, and we here take the opportunity to explicitly show that the data reported in the supplementary material of reference 5 are actually fully consistent with our results and interpretation. Based on electronic structure calculations, in our original work[2] we assigned the character of the IR bands of the reactants that were subject to vibrational strong coupling experiments in references 4 and 5. For the case of the reaction reported in reference 5, the reactant's IR band at ~1100 cm^{-1} was assigned to a Si-O stretching band in the experimental paper.[5] In contrast, our calculations indicate that this band is due to a pure C-O stretching mode while the Si-O stretching vibration contributed to several modes in the 500-900 cm^{-1} region.[2]

In Figure 1 (top), we show the experimental IR spectra of the reactant and products **1** and **2** (P_{CH} and P_{OH}, respectively) that were reported in the supplementary material of reference 5. The IR region centered at 1100 ± 20 cm^{-1} is highlighted in grey. In the comment on our work, the authors state that: "Since the Si-O cleavage reaction results in a product that no longer contains a Si-O bond, the absence of the 1110 cm^{-1} band in the IR spectrum of [product] **2** clearly shows that the 1110 cm^{-1} band is mainly associated with the Si-O stretch of product **1**".[1] Although it is true that product **2** has no peak at 1100 cm^{-1}, the results reported in our original manuscript and its supplementary material indicate that this is because the **C-O** stretching band in this product is slightly red-shifted to the 1020-1060 cm^{-1} region (highlighted in yellow).[2] Such a shift is expected in product **2** since the functional group, which is an alcohol (**C-O**-H), is different to that of the reactant and product **1**, which is a silyl ether (Si-**O-C**). As clearly shown in Figure 1, the ~1100 cm^{-1} band we calculate for the reactant and product **1** matches the experimental one and the red-shifted band of product **2** (highlighted in yellow) is also captured by our calculations. In conclusion, visualization of the normal modes of the three species and comparison with the experimental spectrum strongly suggests that the bands at ~1100 cm^{-1} in the reactant and product **1** and at ~1040 cm^{-1} in product **2** are due to the C-O stretching and not the Si-O stretching.

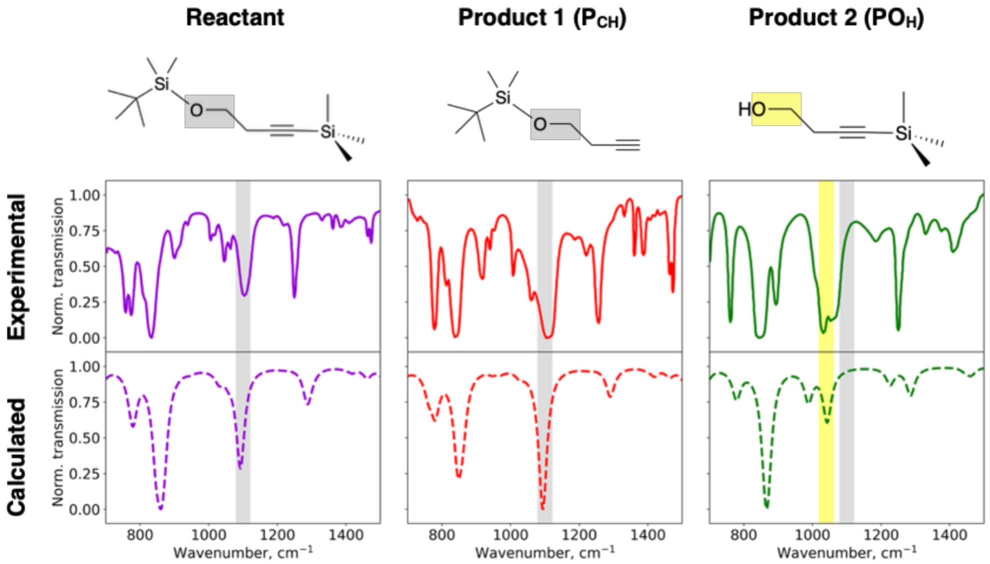

Figure 1. Experimental (top) and calculated (bottom) IR spectra of the reactant (left) and both products (middle and right) of the reaction reported in references 5 and 2. Computational details can be found in reference 2.

In contrast to the claim raised in the comment that “Since there are differences between our results and their calculations, they assume that our assignments are wrong”,[1] we again stress that our electronic structure calculations are consistent with the experimental results, and our paper does not imply or claim that any of these results are wrong. We simply used the combined information from experiment and calculations to obtain further insight and improve the assignments made initially.

In addition to the above considerations, we would like to stress that electronic structure calculations are well-established tools and often play an essential role both in understanding reaction mechanisms and in the interpretation of molecular IR spectra.[14-30] We would also like to point out that rather than there being “no consensus about the details of the mechanism”, each S_N2 reaction has its own intrinsic features, and molecularly detailed calculations are particularly useful to understand these features.[31–38] As already stated in our original work,[2] our results on the reaction mechanism are consistent with the experimentally observed kinetics. The goal of these calculations is not to achieve exact quantitative agreement with experiment, but rather to obtain chemical insight into the reaction mechanism. We also emphasize that all our calculations were carried out with a polarizable continuum solvation model, such that dielectric constant-induced solvent effects are indeed included in our results. Note that these are the principal solvent effects affecting the reaction profile and the activation barrier. Although hydrogen bonding can modify the relative stability of some species in S_N2 reactions, these are secondary effects compared to the electronic structure dictated by the forming and breaking of covalent bonds that determine the global shape of the potential energy surface along which the reaction takes place.[32,34,35,39]

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