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Polaritonic Chemistry

Direct Observation of Polaritonic Chemistry by Nuclear Magnetic Resonance Spectroscopy

B. Patrahau⁺, M. Piejko⁺, R. J. Mayer, C. Antheaume, T. Sangchai, G. Ragazzon, A. Jayachandran, E. Devaux, C. Genet, J. Moran,^{*} and T. W. Ebbesen^{*}

Abstract: Polaritonic chemistry is emerging as a powerful approach to modifying the properties and reactivity of molecules and materials. However, probing how the electronics and dynamics of molecular systems change under strong coupling has been challenging due to the narrow range of spectroscopic techniques that can be applied in situ. Here we develop microfluidic optical cavities for vibrational strong coupling (VSC) that are compatible with nuclear magnetic resonance (NMR) spectroscopy using standard liquid NMR tubes. VSC is shown to influence the equilibrium between two conformations of a molecular balance sensitive to London dispersion forces, revealing an apparent change in the equilibrium constant under VSC. In all compounds studied, VSC does not induce detectable changes in chemical shifts, J-couplings, or spin-lattice relaxation times. This unexpected finding indicates that VSC does not substantially affect molecular electron density distributions, and in turn has profound implications for the possible mechanisms at play in polaritonic chemistry under VSC and suggests that the emergence of collective behavior is critical.

Introduction

Vibrational strong light-matter coupling (VSC) has emerged as an innovative approach for influencing molecular properties and chemical reactivity.^[1,2] In VSC, molecular vibrational transitions are strongly coupled to the zero-point electromagnetic fluctuations of an infrared cavity. Under the

right conditions, this interaction gives rise to two hybrid light-matter vibropolaritonic states (VP+ and VP−) along with N-1 dark collective states (DS) resulting from the coupling of N molecules with the optical mode (Figure 1). The formation of these hybrid states, which occurs in the dark, has been shown to alter reaction rates,^[3–14] chemical selectivity,^[12–14] electrochemical modulation,^[15] charge transfer equilibria^[16] and many other properties such as ionic conductivity,^[17,18] electrical conductivity,^[19] crystallization^[20] or self-assembly.^[21,22]

Despite the numerous experimental studies of chemistry and properties under VSC^[1–29] and extensive theoretical studies,^[30–50] a detailed understanding of the underlying processes is still lacking. Systematic experimental studies on a variety of molecular systems should help constrain the different models and to extract general principles for how VSC influences chemistry. The experiments are challenging because they require knowledge of both optics and chemistry. Studying chemical reactivity correctly can be daunting in a normal situation but even more so in the constrained conditions of a cavity which are typically followed on the minute time scale. At such slow rates, the presence of the smallest amount of impurities can affect the outcome. So it is perhaps not surprising that two reactions under VSC were found not to be reproducible^[9,28] out of about 16 reported so far.^[1,3–8,10–13,20] In addition, changes in kinetics will only be detected if VSC affects the rate limiting

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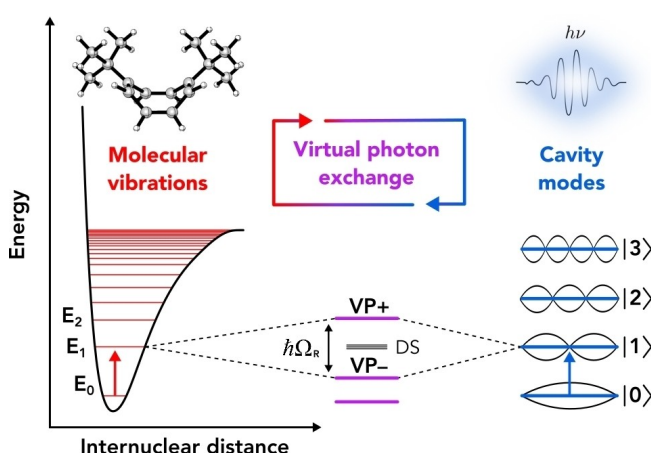


Figure 1. Schematic diagram of the formation of vibro-polaritonic states. VP+ and VP− are the upper and lower bright vibropolaritonic states and DS degenerate dark states from resonant vibrational and optical transitions.

step and so some reactions are just not affected by VSC.^[27,29] It is therefore important to not just rely on kinetic studies but also monitoring product yields and composition. For this purpose, NMR would be ideal but it is challenging in view of the small quantities in cavities. Furthermore, the cavities used for VSC are typically composed of two parallel mirrors (Fabry-Perot resonators) that are tuned at normal incidence ($k_{\parallel}=0$) by compressing a polymer spacer which, in turn, deforms the mirrors. The resulting cavity is, therefore, tuned only within a small sweet spot through which spectroscopic analysis must be carried out. In addition, the high reflectivity of the mirrors complicates spectroscopy in the IR and UV/Vis regions. These aspects make it difficult to experimentally probe how VSC influences chemistry, impact the reproducibility of VSC studies, and constitute barriers to entry for scientists unfamiliar with optics.

Results and Discussion

In response to these challenges, we have developed a new type of Fabry-Perot (FP) cavity in a microfluidic chip designed for VSC that can be used easily by non-specialists (Figure 2). These cavities are compatible not only with the previously used spectroscopic methods but, most importantly, the chemistry can be directly monitored by standard liquid Nuclear Magnetic Resonance (NMR) spectroscopy following a protocol we have developed for this purpose. This gives VSC experiments access to the full power of NMR spectroscopy, currently one of the most important and widely used analytical techniques in chemistry, enabling a direct and detailed characterization of a broad range of chemical and biological systems.

The potential of these new NMR-compatible cavities is illustrated by direct observation of the VSC-induced modification in a molecular balance that interconverts between two conformations at thermodynamic equilibrium. This equilibrium is known to be a probe of intramolecular London dispersion forces.^[51] Importantly, the NMR spectra of this compound and other compounds studied under VSC show surprisingly that the chemical shifts, the J-couplings, and the spin-lattice relaxation time (T_1) remain unchanged under VSC. These observations enabled by the new cavities give insight into the mechanism of VSC and indicate that redistribution of electronic density is not the major cause of changes in chemical reactivity, solvent polarity, and molecular assembly under VSC, as chemists would have expected.

At the outset of the cavity design, it was not clear whether NMR signals could be measured inside a microfluidic FP cavity. After all, a typical FP cavity formed with metallic gold mirrors separated by 10 μm might be a Faraday cage for the 500 MHz (0.6 m) frequency used to probe nuclei in a standard NMR spectrometer. To facilitate the measurements and allow for widespread adoption of the technique, the cavities should fit inside a standard tube normally used for liquid NMR spectroscopy ($\varnothing 5\text{ mm}$). Additionally the FP cavity should have the same resonance wavelength everywhere across the microfluidic channel. To meet these challenging requirements, FP cavities were fabricated to our specifications by Lionix International, a specialized manufacturer of microsystems from which they can be purchased. After several iterations, the FP cavities were made in both fused silica and Si substrates as they each have their distinct advantages. The former is transparent in the UV and visible region but opaque below 2000 cm^{-1} while the latter is opaque across the UV/Vis but transparent across the IR region of interest down to 500 cm^{-1} . Figure 2a shows the

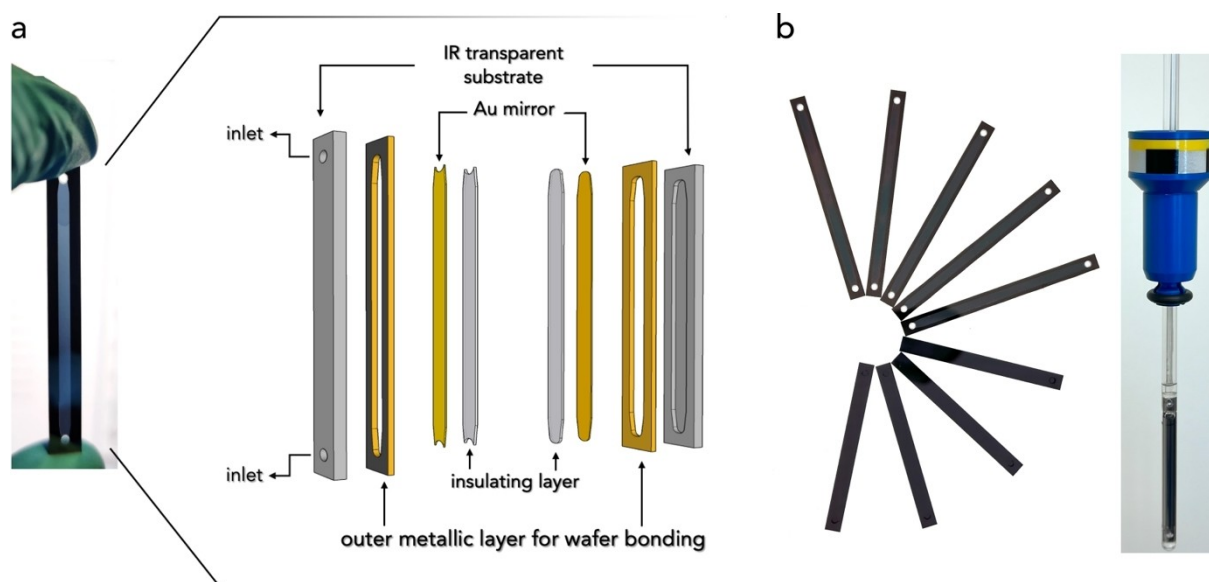


Figure 2. Microfluidic cavities compatible with NMR spectroscopy. (a) Photograph of a cavity being filled with liquid along with its cross-section. (b) A set of NMR compatible cavities of different pathlengths and an NMR tube containing a sealed cavity immersed in deuterated water and plastic holders used to center the cavity inside the tube.

cross-section and a photograph of a typical NMR-compatible FP cavity. Channels $\sim 10\ \mu\text{m}$ deep were etched into the substrate of choice, followed by deposition of 5 nm of Cr and 10 nm Au. To bond the top mirror to the bottom substrate bearing the channel, 200 nm Au was deposited on the substrate surface and the two parts were press-welded. The channel is 4 cm long but only 2 mm wide to ensure flatness across the width. IR spectroscopy shows that the resonance varies by less than $3\ \text{cm}^{-1}$ for a mode at $3038\ \text{cm}^{-1}$, implying that the path length is essentially constant everywhere in the channel (see Figure S5 and details in Supporting Information) with full width at half max (FWHM) around $60\text{--}80\ \text{cm}^{-1}$ and Q factors of ~ 10 . In the case of the cavities prepared in Si substrates, a SiO_x layer (100 nm) was also added to protect the Au mirrors from reactive agents. A set of cavities in both silica and Si are shown in Figure 2b. The silica cavities can be characterized in the UV/Vis for changes in absorbance or fluorescence. Angular dispersion curves can easily be recorded, since the new cavity geometry does not hinder the light passing through the sample at a wide angle.

For NMR measurements, the following protocol was established to collect signals of reproducible quality. The cavity must be centered in the NMR tube using a 3D-printed holder to ensure proper shimming (magnetic field homogeneity). Proper shimming is the most challenging step. The scarce amount of intracavity material (about $1\ \mu\text{L}$ of solution) makes it impossible to properly lock on to the NMR signal, and so the cavity is immersed in deuterated

solvent, such as D_2O , which may additionally contain an external standard (e.g. dimethyl sulfone). To avoid any interaction with the outer deuterated solvent the holes used to insert the compound into the cavity must be sealed before introducing the cavity in the NMR tube. Furthermore, it became quickly clear that orientation of the cavity inside the spectrometer is also critical, and a long plastic holder was fabricated to ensure that the cavity is in optimal orientation relative to the probe field (Figure 2b and section 4 and 5 in the SI). To enhance the low intensity of intracavity signals various solvent suppression pulse sequences can be used.

Figure 3 shows the ^1H NMR and ^{13}C NMR spectra of neat 1,2-diethylbenzene recorded in cavities being on and off resonance with the C–H stretching band. The Rabi splitting is estimated to be ca. $150\ \text{cm}^{-1}$ (see Figure S15). Despite the potential challenges already discussed, a good-quality signal can be obtained in the FP cavity. Perhaps most surprisingly, when the different vibrational bands of these molecules are strongly coupled to the cavity mode, no changes in chemical shifts are detected by ^1H NMR and ^{13}C NMR, the latter being much more sensitive to electron density changes. This observation holds for all other compounds and solvents that have thus far been tested. Since ^{19}F NMR is even more sensitive than ^{13}C NMR, we also tested a 1:1 mixture of 1*H*,1*H*-tridecafluoro-1-heptanol and 1,4-difluorobenzene with the C–F stretching mode under VSC but again any changes are within the experimental error (see section 7 of SI). This implies that the electron density redistribution caused by VSC must be on

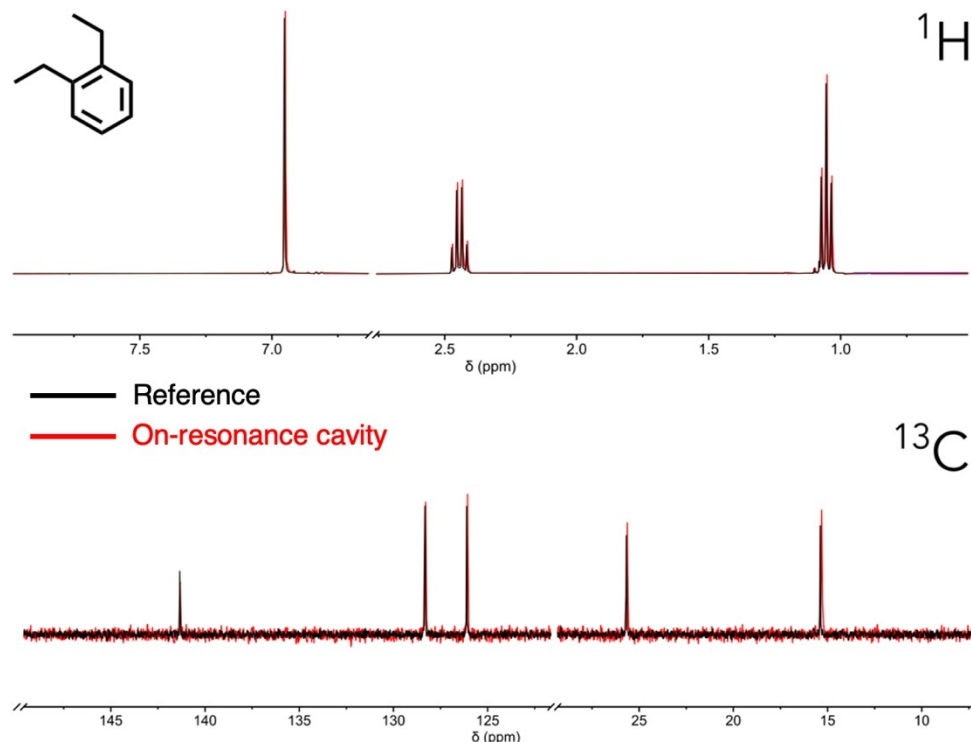


Figure 3. ^1H and ^{13}C NMR spectra of neat 1,2-diethylbenzene in a reference insert tube (black) and in a cavity (red) in which the ^{13}C optical mode is strongly coupled to the C–H stretching vibrational band.

average very small, to the point of being undetectable by NMR and is thus unlikely to be responsible for the observed changes in octanol polarity under VSC. Similarly, the fine structure coupling constant and spin-lattice relaxation time remain unchanged under VSC (see section 7 in the SI). These findings are very significant in that they narrow the possible explanations as to why VSC induces changes in chemical processes, which will be discussed further down.

To prove the potential of NMR spectroscopy as a technique of choice for polaritonic chemistry, the NMR compatible cavities are used to directly probe the VSC-induced modification of London dispersion forces. For this purpose, we set out to study the conformational equilibrium of a molecular balance (**1**), an established system for studying London dispersion forces in solution.^[51] **1** consists of a cyclooctatetraene core bearing two *tert*-butyl moieties and exists in two conformations in which the *tert*-butyl groups are oriented towards or away from one another (named *folded* and *unfolded*, respectively – see Figure 4a). As demonstrated by Schreiner et al.,^[51] the folded conformer is stabilized by London dispersion forces between the two *tert*-butyl groups. In contrast, the *tert*-butyl groups are too far away from each other in the unfolded conformer to interact in an intramolecular fashion. The fact that the balance does not have any polarized functional groups, but

is instead purely hydrocarbon-based is advantageous since it simplifies the behavior of the system as well as data interpretation.

To study the effect of VSC on the mentioned equilibrium, we synthesized this molecular balance and compared the equilibrium constant of the molecular balance in solutions of varying concentrations in deuterated benzene. The equilibrium constant is determined from peak areas of ¹H signals corresponding to both folded and unfolded conformers. The peak areas are obtained by either directly integrating signals areas or line shape fitting in the quantitatively measured ¹H NMR spectrum. The peak assignment and equilibrium constant determination is based on the data provided in the original study by Schreiner et al.^[51]

$$K = \frac{C_{\text{folded}}}{C_{\text{unfolded}}} = \frac{\int_{\text{folded}}}{\int_{\text{unfolded}}} \quad (1)$$

where C_{folded} , C_{unfolded} are the concentration of the folded and unfolded conformers and \int_{folded} , \int_{unfolded} are the peak areas of the ¹H signals of both conformers respectively.

First, we studied the equilibrium at low concentration (100 mM in benzene-*d*₆) in a standard NMR tube insert at 23 ± 1 °C. The determined value of the equilibrium constant

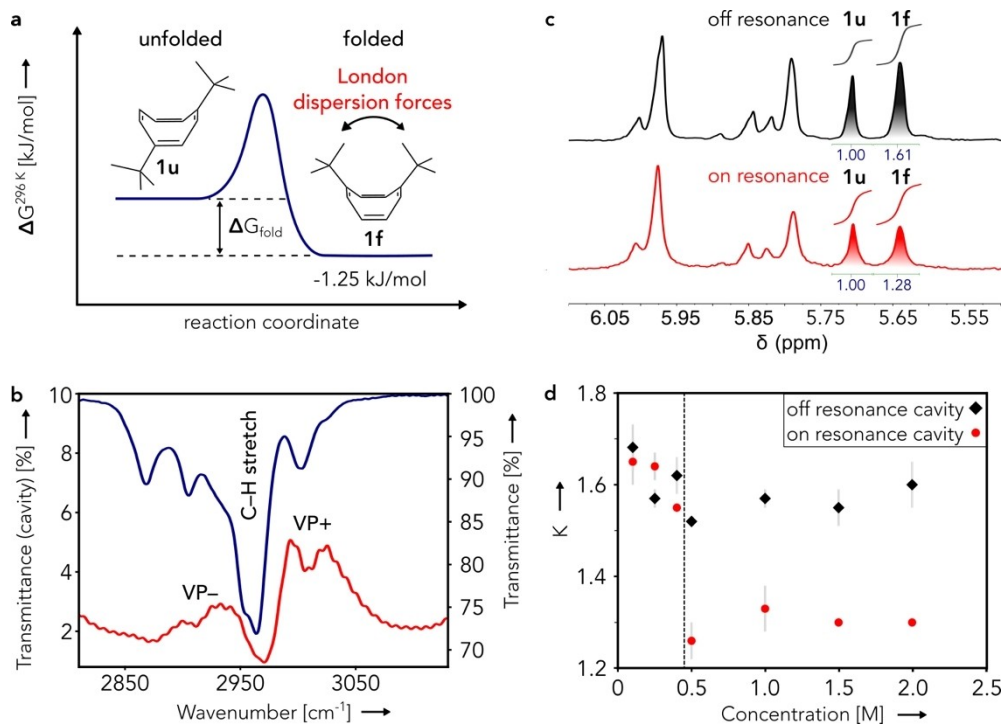


Figure 4. Influence of VSC on the London dispersion forces-driven equilibrium. (a) The cyclooctatetraene-based molecular balance (**1**) exists in two distinct conformations (unfolded and folded). The ΔG_{fold} value is for the molecular balance in benzene-*d*₆. (b) FT-IR spectrum of the neat molecular balance measured by ATR (navy blue) and a transmission-mode spectrum of a 1 M solution of the molecular balance in benzene-*d*₆ in a cavity in which the 11th Fabry-Perot mode is resonant with the C–H stretching mode at 2970 cm⁻¹ showing the formation of two vibropolaritonic bands (VP– and VP+). The Rabi splitting at this concentration is ca. 83 cm⁻¹. The cavity spectrum was smoothed using the moving average method to remove artifact interference (see Figure S7). (c) Partial ¹H NMR spectra of a 1 M solution of **1** in benzene-*d*₆ of the molecular balance in an off-resonance (black) or on-resonance (red) cavity. The shaded peaks originate from the same ¹H in the two different conformations (d) The concentration profile of the equilibrium constant (K) of the molecular balance in benzene-*d*₆ in cavities that are off and on resonance with the C–H stretching vibration (black and red datapoints, respectively). The error bars correspond to the standard error at each point.

(1.64 ± 0.01) is in agreement with the data reported by Schreiner and co-workers (1.71, extrapolated using the van't Hoff equation for 23 °C, see the SI) and corresponds to $\Delta G_{\text{fold}} = -1.36$ kJ/mol. Next, cavities with two different path lengths were chosen that are either off-resonance or on-resonance with the C–H stretching band of the molecular balance at 2970 cm^{-1} . It is important to note that strong coupling in the on-resonant cavities can only be reached above a certain concentration threshold when the concentration is sufficient to ensure that the exchange of virtual photons between the cavity mode and the molecules is faster than any dissipative process.^[1,2] In the off-resonance scenario, by increasing the concentration by up to 2 M, no change in the value of the equilibrium constant was observed. The value was identical (within experimental error) in the case of the on-resonance cavity at low concentration when there is still no strong coupling. However, upon reaching the strong coupling condition at ca. 0.5 M, the equilibrium constant decreased sharply to a value of 1.26 ± 0.04 , which corresponds to $\Delta G_{\text{fold}} = -0.57$ kJ/mol. Interestingly, the value remained fairly constant (within experimental error – see section 16 in the SI) in solutions of higher concentration up to 2 M despite the fact the Rabi splitting increases as square root of the concentration and thereby increasing the number of coupled molecules in solution. This phase transition-like behavior (Figure 4d) is similar to the one described in previous work.^[16]

The behavior of the molecular balance is direct evidence that VSC alters London dispersion forces and confirms our suggestions inferred from previous experiments^[16] as well as theoretical predictions^[52–54] and other indirectly related experimental studies.^[23] The VSC-induced reduction of the equilibrium constant, and therefore, smaller Gibbs free energy difference between the two conformers implies that intramolecular dispersion forces are weaker under strong coupling. Outside cavity conditions, it is reported that the solvent reorganization entropy affects the dispersion interactions in the studied molecule whereas the dispersion enthalpy remains constant upon changing the solvent.^[51] The modification of solvent properties under VSC might therefore derive from changes to solvation entropy due to N-1 dark states which appear when N molecules are coupled to a given optical mode,^[55] as in these experiments. The details of the various contributions are beyond this study and would benefit from further theoretical analysis.

It should be noted that again in studying the molecular balance **1**, no changes in chemical shifts despite signal broadening in some cases due to worse homogeneity of the sample are observed under VSC and despite the modification of the chemical equilibrium and the dispersion forces. More generally, considering the large effects of VSC on chemical reactivity, solvent polarity, aggregation, and other findings, a significant chemical shift would naturally be expected. After all, a change in chemical reactivity, induced for example by functionalization, is typically associated with a change in electron density distribution in the reactant molecule which then shows up in the chemical shifts. The fact that it does not, implies that other factors are at play, in particular the emergence of collective behavior under VSC.

A chemical reactivity landscape is a multidimensional space along the various possible nuclear coordinates. Reactions proceed via the lowest energy coordinate which typically involves coupling between a vibrational mode and the electronic manifold. Chemical reactivity changes observed under VSC are very sensitive to the symmetry of the vibrations that are strongly coupled because vibronic coupling is itself very sensitive to symmetry.^[14,16] Upon VSC, the hybrid vibropolaritonic mode has a different symmetry than the bare vibration and thereby affects the normal pathway. If the low energy pathway is hindered by this symmetry change, the new transition state will occur at a different crossing, which in turn would lead to large changes in the activation energy as observed experimentally.^[3,13] This is likely one of the reasons for the modified activation energies of reactions under VSC.

The concentration profile of the equilibrium constant for the dispersion molecular balance shown in Figure 4d suggests the emergence of collective molecular behavior at the onset of VSC, i.e. at the onset of VSC and the generation of collective vibropolaritonic states as discussed in the introduction, the properties change but afterwards remain constant with increasing concentration. Similar phase-transition like behavior has already been reported.^[16] Strong coupling of a significant fraction of the molecules at the onset of VSC appears to pull nearly all the molecules into one phase by dipolar interactions due to the zero-point field oscillations of the optical mode. This collective coupling competes with the molecular dynamic disorder inherent in the solution. Nevertheless, the collective phase will affect solvation and solute-solvent interactions, either stabilizing or destabilizing the solute. The solvent molecules re-organize on a time-scale much faster than that of the NMR measurement. Finally, the observed effects of VSC on solvation-sensitive processes such as ionic conductivity,^[17,18] self-assembly^[21,22] and crystal polymorphism^[20] are no doubt also related to the emergence of collective behavior and its effect on solute-solvent interactions. For instance, electrochemical experiments show that the modification of ionic conductivity correlates well with changes in hydration and hydration entropies under VSC.^[17] Recent theoretical studies also point to the role of “polarization” effects where individual molecules are polarized by the collective strong coupling^[52–54,56] (both ESC and VSC) which fits the current findings, except that they do not induce significant charge redistribution.

In a system totally different from the molecular balance in this study, it was shown that charge transfer equilibria under VSC can be tilted one way or the other by simply coupling vibrations of different symmetries.^[16] In this specific case, one would still expect electronic density redistribution that should be studied by NMR. Nevertheless, the observed changes in the Gibbs free energies in the previous study^[16] imply that the intermolecular interactions with the solvent and thereby the solvation energies are strongly modified. The emergence of collective behavior under VSC was also observed which may include potentially large changes in entropy.^[55] Furthermore the entropy of equilibria is itself symmetry-dependent.^[57] Rovibrational

averaging is known to affect electronic properties such as chemical shifts and this averaging will no doubt be modified by the formation of hybrid vibropolaritonic modes and may contribute to the effects seen under VSC.

Finally, it should be noted that NMR gives access to a wide variety of experiments that give insight into chemical systems such as T2 (spin-spin) relaxation times, Diffusion Ordered Spectroscopy (DOSY) or other two-dimensional techniques. Each experiment might hold its own limitations when using optical cavities due to factors such as signal intensity or sample homogeneity. These are however beyond the scope of this paper and should be addressed in future studies.

Conclusions

The development of the NMR-compatible cavities allowed us to directly observe the modification of London dispersion forces under VSC with a molecular balance. NMR also provides key insight into the possible mechanisms at play in VSC. The expected VSC-induced charge redistribution are so small that they cannot account for the large property changes. Clearly the emergence of collective behavior and the subsequent modification of solute-solvent interactions, together with changes in vibronic coupling and entropy which are symmetry dependent, are at the heart of the observed effects of VSC. The ability to observe chemistry under VSC by in situ NMR unlocks the study of a variety of chemical systems that would otherwise be inaccessible and should further improve the fundamental understanding of polaritonic chemistry.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: NMR · vibrations · strong coupling · dispersion forces

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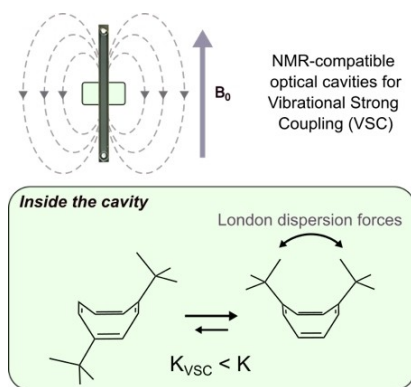
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Research Articles

Polaritonic Chemistry

B. Patrahau, M. Piejko, R. J. Mayer,
C. Antheaume, T. Sangchai, G. Ragazzon,
A. Jayachandran, E. Devaux, C. Genet,
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Direct Observation of Polaritonic Chemistry
by Nuclear Magnetic Resonance Spectroscopy



New Fabry-Perot optical cavities were developed that enable studying Vibrational Strong Coupling (VSC) by Nuclear Magnetic Resonance (NMR) spectroscopy. We demonstrate that the London dispersion-driven conformational equilibrium of a molecular balance is altered when the C–H stretching vibration is strongly coupled to the cavity. Unexpectedly, VSC does not substantially affect molecular electron density distributions which has profound implications for the possible mechanisms at play in polaritonic chemistry.