

Entangled Photon Spectroscopy

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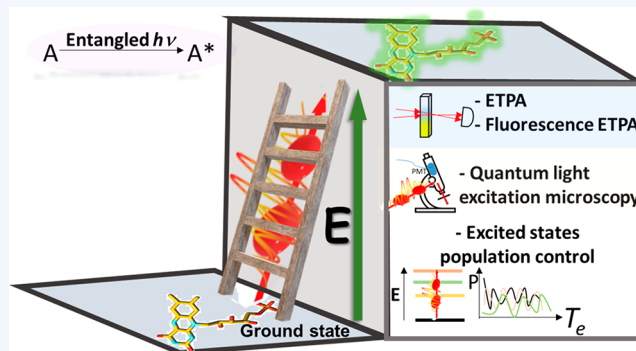
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CONSPECTUS: The enhanced interest in quantum-related phenomena has provided new opportunities for chemists to push the limits of detection and analysis of chemical processes. As some have called this the second quantum revolution, a time has come to apply the rules learned from previous research in quantum phenomena toward new methods and technologies important to chemists. While there has been great interest recently in quantum information science (QIS), the quest to understand how nonclassical states of light interact with matter has been ongoing for more than two decades. Our entry into this field started around this time with the use of materials to produce nonclassical states of light. Here, the process of multiphoton absorption led to photon-number squeezed states of light, where the photon statistics are sub-Poissonian. In addition to the great interest in generating squeezed states of light, there was also interest in the formation of entangled states of light. While much of the effort is still in foundational physics, there are numerous new avenues as to how quantum entanglement can be applied to spectroscopy, imaging, and sensing. These opportunities could have a large impact on the chemical community for a broad spectrum of applications.

In this Account, we discuss the use of entangled (or quantum) light for spectroscopy as well as applications in microscopy and interferometry. The potential benefits of the use of quantum light are discussed in detail. From the first experiments in porphyrin dendrimer systems by Dr. Dong-Ik Lee in our group to the measurements of the entangled two photon absorption cross sections of biological systems such as flavoproteins, the usefulness of entangled light for spectroscopy has been illustrated. These early measurements led the way to more advanced measurements of the unique characteristics of both entangled light and the entangled photon absorption cross-section, which provides new control knobs for manipulating excited states in molecules.

The first reports of fluorescence-induced entangled processes were in organic chromophores where the entangled photon cross-section was measured. These results would later have widespread impact in applications such as entangled two-photon microscopy. From our design, construction and implementation of a quantum entangled photon excited microscope, important imaging capabilities were achieved at an unprecedented low excitation intensity of 10^7 photons/s, which is 6 orders of magnitude lower than the excitation level for the classical two-photon image. New reports have also illustrated an advantage of nonclassical light in Raman imaging as well.

From a standpoint of more precise measurements, the use of entangled photons in quantum interferometry may offer new opportunities for chemistry research. Experiments that combine molecular spectroscopy and quantum interferometry, by utilizing the correlations of entangled photons in a Hong–Ou–Mandel (HOM) interferometer, have been carried out. The initial experiment showed that the HOM signal is sensitive to the presence of a resonant organic sample placed in one arm of the interferometer. In addition, parameters such as the dephasing time have been obtained with the opportunity for even more advanced phenomenology in the future.



KEY REFERENCES

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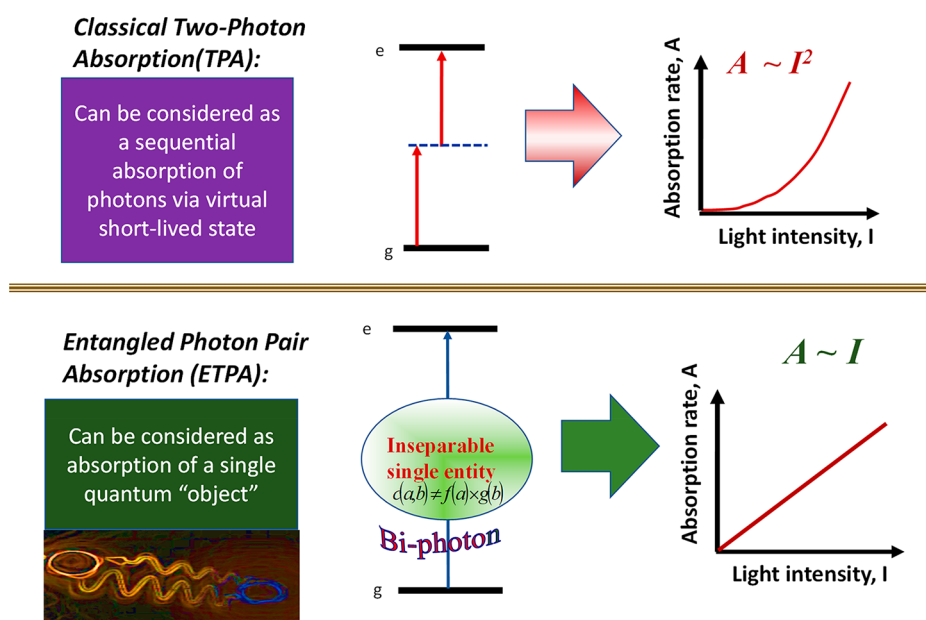


Figure 1. Schematic representation of the absorption process for the entangled photon pair in comparison with two-photon absorption of classical light. Depiction of the biphoton as a single entity is shown on the left.

- Varnavski, O.; Pinsky, B.; Goodson, T., III Entangled Photon Excited Fluorescence in Organic Materials: An Ultrafast Coincidence Detector. *J. Phys. Chem. Lett.* **2017**, *8*, 6–11.² Demonstrating the ability to measure entangled two-photon excited fluorescence in a range of organic molecules. This study includes multiple tests showing the entangled origin of the measured fluorescence signal.
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- Eshun, A.; Gu, B.; Varnavski, O.; Asban, S.; Dorfman, K. E.; Mukamel, S.; Goodson, T., III Investigations of Molecular Optical Properties Using Quantum Light and Hong–Ou–Mandel Interferometry. *J. Am. Chem. Soc.* **2021**, *143*, 9070–9081.⁴ This experiment combines molecular spectroscopy and quantum interferometry, using the correlations of entangled photons in an HOM interferometer to study molecular properties. The HOM signal is sensitive to the resonant organic sample and contains information about the light–matter interaction.

1. INTRODUCTION

Recent interest in the use of chemical systems under the context of quantum information science has inspired new approaches to creating novel molecules and spectroscopic probes. Both theoretical and experimental findings have been directed at useful applications of these molecules and probes for enhanced sensing and new information regarding the electronic interactions with quantum light.^{5–7} As it has been observed previously in atomic systems, nonclassical light may result in an enhanced precision and resolving power of conventional measurement techniques beyond the shot noise

limit.^{8–11} For the case of photon number squeezing, it has been shown that optical measurements could be performed below the classical limit for a particular sensing methodology. Different approaches for sensing utilizing quantum entangled photons were later reported, suggesting enhanced resolving power in spectroscopy and imaging and later in interferometry. To date, nonclassical states of light have been applied to new computing, communication, and imaging technologies.^{12–14}

Utilizing nonclassical states of light to probe optical properties in molecules provides several potential advantages as compared to classical light. For example, quantum entangled light generated in the form of photon pairs has a high degree of temporal and spatial correlations that present it as a powerful sensing tool.^{15,16} Utilizing the unique features of entangled photon pairs, one may also pursue the possibility of targeted coherent control of photochemical processes.^{17,18} The photon pairs, created under spontaneous parametric downconversion, illustrate unique low noise characteristics compared to classical photons. In the context of imaging (in biological systems), the highly correlated light provides the opportunity to probe chemical and biological systems at extremely low photon flux, avoiding the typical light toxicity detrimental issue.¹⁸ Measurements may be achievable with sensitivity beyond the standard quantum limit, and limitations of low signal-to-noise ratio and resolution can be overcome while exciting photosensitive materials. Furthermore, the frequency and polarization correlations of entangled light can be used to conduct spectroscopy in new spectral ranges. It is also important that key entanglement characteristics of nonclassical light have been shown to maintain after propagating through relatively thick, turbid biological samples.^{19,20}

Recent advances in understanding and manipulating of quantum light have led to its growing use as a spectroscopic tool. Of particular focus to this account is the initial and growing interest and development of measurements of the entangled two-photon absorption (ETPA) process in organic materials. From the initial theoretical and experimental illustrations of ETPE to the application in fluorescence,

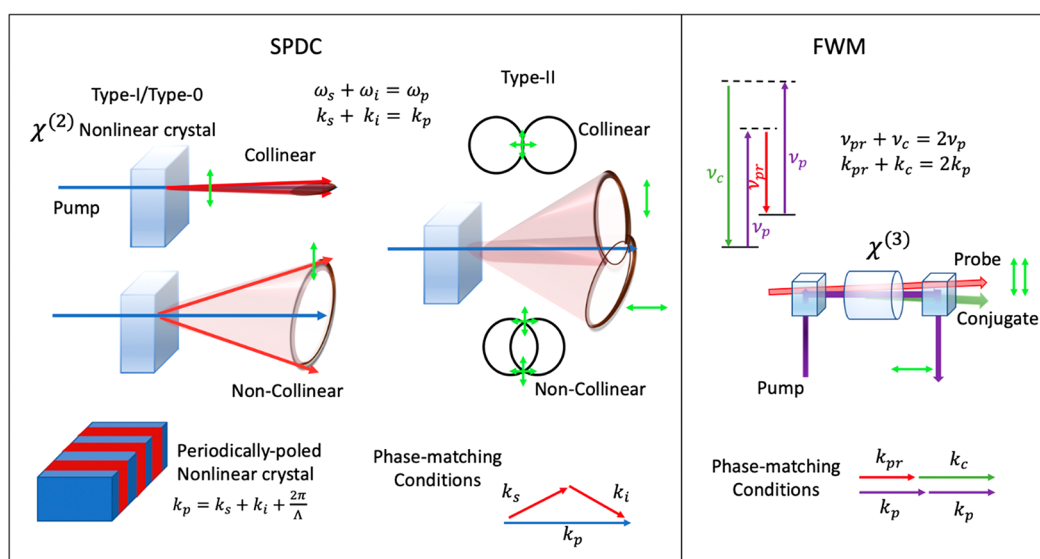


Figure 2. Diagram of nonclassical light sources. On the left, SPDC with a $\chi^{(2)}$ bulk crystal showing the cone-like spatial arrangement of signal and idler photons for type-I/0 and -II SPDC and a periodically poled crystal (bottom left) with quasi phase-matching properties. The phase-matching conditions determine the angular spread of SPDC photons as the pump beam direction is varied with respect to the crystal's optical axis. This causes the cone-like emission. On the right, the phase matching conditions, and diagram of the four wave mixing (FWM) process are shown as well as an energy diagram of the involved beams.

biophysics, and interferometry, there is great excitement surrounding this process and its development.^{1,7,8,11,21–24} We will discuss in-depth the experimental data on ETPA, what has been achieved with entangled photon fluorescence measurements, the use of entangled photon pairs in biological applications, as well as looking into new spectroscopic methods involving quantum interferometry.

2. TYPES OF QUANTUM LIGHT GENERATION

Nonclassical or quantum light is generally explained as that which cannot be described with classical electromagnetism and must be described by the quantized electromagnetic field. As such, quantum and classical light differ in terms of their statistics, correlations, and fluctuations. Looking at photon statistics for nonclassical light in terms of light fluctuations, the nature of nonclassical light allows for much lower fluctuations in photon number, which becomes useful in enhancing signal-to-noise ratio in measurements.²⁵ These distribution statistics can in turn be correlated to the coherence properties of light. For classical light, photon modes are statistically independent, while for nonclassical light, the temporal correlations ensure that the arrival of one photon is followed by the arrival of the corresponding entangled photon. These strong temporal correlations allow entangled photons to be useful for measurements via interference, coincidence detection, quantum reconstruction, and entangled two-photon absorption.²⁶

Qualitatively, the entangled photon pair can be considered as a single quantum object interacting with matter. In the case of entangled photon absorption, the absorption of this single quantum entity (photon pair) leads to a linear scaling (rather than quadratic for nonentangled light) in photon flux (Figure 1). This mechanism ensures enhanced two-photon absorption (and fluorescence) efficiency in the process.

Due to photon time correlations, the arrival of one photon is followed almost simultaneously by the arrival of its partner, and as a result, both photons of the pair are simultaneously absorbed. This process is dependent on the material electronic

states along with the material dipole moments of the molecule under study. For some molecules, there is an intermediate or virtual state close to resonance with the absorbed photon. In this case, the first photon initiates a transition to this intermediate state, then its sister photon completes the transition to the final state. On the other hand, molecules with intermediate states far off from resonance undergo TPA through direct coupling of the intermediate states to the ground and final states. Hence, there is no intermediate transition. In ETPA, the photon and the material systems are entangled, allowing for better control of excitation pathways. Additionally, the spectral bandwidth and time delay of entangled photons are not Fourier conjugates. Thus, this characteristic that violates classical time and frequency inequalities can be overcome and lead to enhanced control of population dynamics with entangled photons.

Currently, the most common method for generating quantum entangled photon pairs is spontaneous parametric downconversion (SPDC). SPDC involves the interaction of a strong pump beam of frequency ω_p , with a $\chi^{(2)}$ nonlinear crystal, resulting in second-order interactions that cause the emission of a pair of lower energy photons (the signal ω_s and idler ω_i photon). Their energy adds up to that of the pump, $\omega_s + \omega_i = \omega_p$, due to energy conservation.^{27,28} In addition to energy conservation, there is the total conservation of momentum defined by the phase-matching conditions of the propagation constants of the interacting photons, $k_s + k_i = k_p$. These phase-matching conditions determine the spatial correlations and arrangement, and propagation direction of the generated photon pair. The correlation properties govern the angular and temporal widths of the coherence function, which in turn determines the coincidence rate of the signal and idler photons.²⁹ The most common nonlinear crystal used for SPDC is β -barium borate (BBO). Several other crystals and parameters are related to the generation of entangled photons and are summarized in Figure 2.^{29–31}

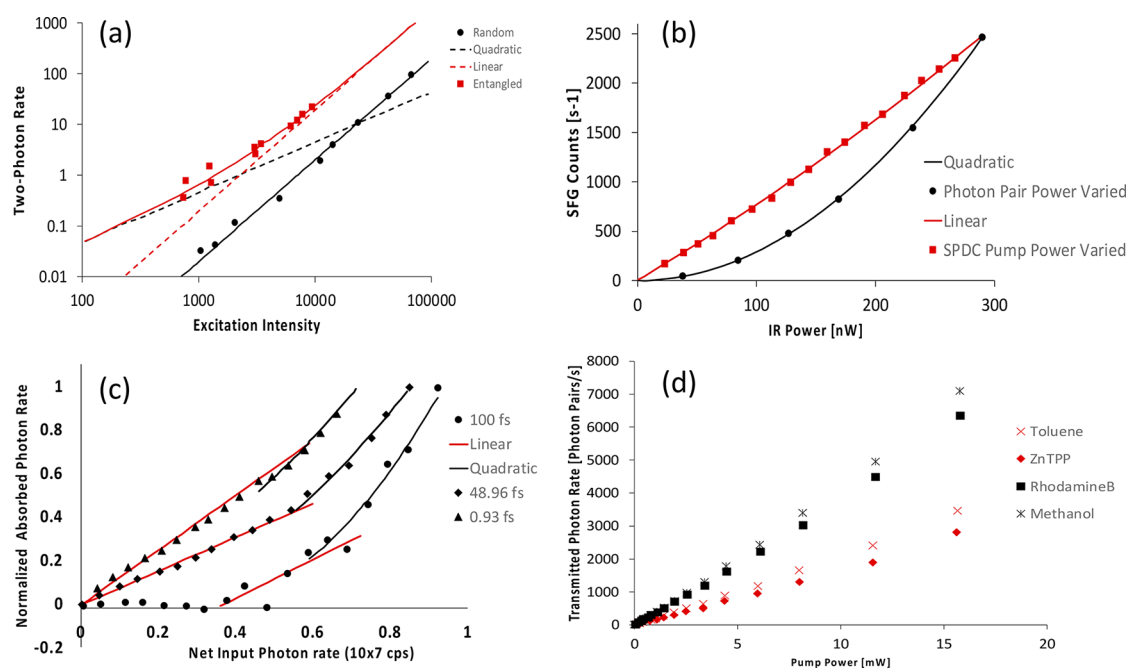


Figure 3. Various plots showing linear ETPA. (a) TPA in atomic Cs with entangled and random (uncorrelated) light.⁹ Adapted with permission from ref 9. Copyright 1995 American Physical Society. Data from ref 9. (b) Sum frequency generation with SPDC photons as a function of power, varying how power is changed.¹¹ Adapted with permission from ref 11. Copyright 2005 American Physical Society. Data from ref 11. (c) ETPA in an organic porphyrin molecule at different entanglement time.¹ Adapted with permission from ref 1. Copyright 2006 American Chemical Society, data from ref 1. (d) Linear ETPA in ZnTPP and Rhodamine B.⁴³ Adapted with permission from ref 43. Copyright 2007 American Chemical Society. Data from ref 43.

3. ENTANGLED TWO-PHOTON ABSORPTION

The nature of nonclassical light and their temporal correlations led researchers to consider the prospects of using entangled light for spectroscopy, specifically, ETPA. Two-photon absorption (TPA) is a widely studied nonlinear process where a molecule directly absorbs two photons and is excited from the ground state to a higher-lying excited state with energy equal to the sum of the absorbed photons.³² The transition probability of this random simultaneous absorption of two photons is proportional to the intensity squared, that is, $R_r = \delta_r \phi^2$, where δ_r is the classical TPA cross-section and ϕ is the photon intensity. Therefore, random TPA needs high optical intensities to occur. Researchers at the Quantum Optics Laboratory at Boston University, who had studied entanglement from SPDC in detail,^{27,29} deduced that since entangled photon pairs are highly correlated in time, absorbing material placed in the beam path would simultaneously absorb both photons of the biphoton pair and ETPA would occur.^{21,22} Due to these strong temporal correlations, the rate of ETPA is linearly dependent on the photon intensity, that is, $R_e = \sigma_e \phi$, where σ_e is the ETPA cross-section and ϕ is the photon intensity (Figure 1).²¹ In addition to the preliminary conceptual studies by Fei et al., a number of theoretical works were published looking at ETPA on atomic systems to study the process of this nonlinear absorption and how it relates to the inherent time difference between the photon pair.^{22,33}

In 1995, Georgiades et al. were the first to observe this linear TPA phenomenon with nonclassical light in an atomic system.⁹ They measured the fluorescence of atomic cesium (Cs) by exciting the atoms with squeezed light generated by parametric down conversion. Interestingly, it was found that there was a deviation from the quadratic dependence of the excited-state

population on intensity expected with classical light, to a function that had a linear plus quadratic fitting function. The log–log plot of the data obtained recorded a slope of 1.3, while the same experiment conducted with classical laser light exhibited the expected classical quadratic behavior (Figure 3a).⁹ They further investigated this by measuring the photocurrent due to the fluorescence from atomic Cs excited by down-converted photons.⁸ Following this novel experimental investigation, Silberberg et al. used the signal and idler beams generated from downconversion in a BBO crystal to excite atomic rubidium and measured the resulting fluorescence with a PMT.¹⁰ The opportunity for quantum coherent control with the TPA process was presented, and it was confirmed that TPA can indeed be induced with down-converted photon pairs at orders of magnitude lower peak power than fs pulses.¹⁰ The nonlinear interactions of entangled photons were tested by measuring the linear dependence of the sum-frequency generation process with entangled photons and how this could become quadratic by altering the photon pair power as opposed to the pump laser power (Figure 3b),¹¹ setting the groundwork for experimental ETPA.

Our initial advances into the realm of quantum optics and materials started with generating photon-number squeezed states by TPA in novel materials. We accomplished this in both an organic polymer and an inorganic semiconductor material embedded in a polymer host, observing strong TPA and a reduction in photon number noise below the shot noise level.^{34,35} Since then, and with the observation of ETPA in atomic systems, our focus shifted toward experimentally realizing ETPA in molecules, as this would allow for major applications involving quantum sensing. In 2006, we conducted the first successful investigations of ETPA in an organic molecule with an organic porphyrin dendrimer

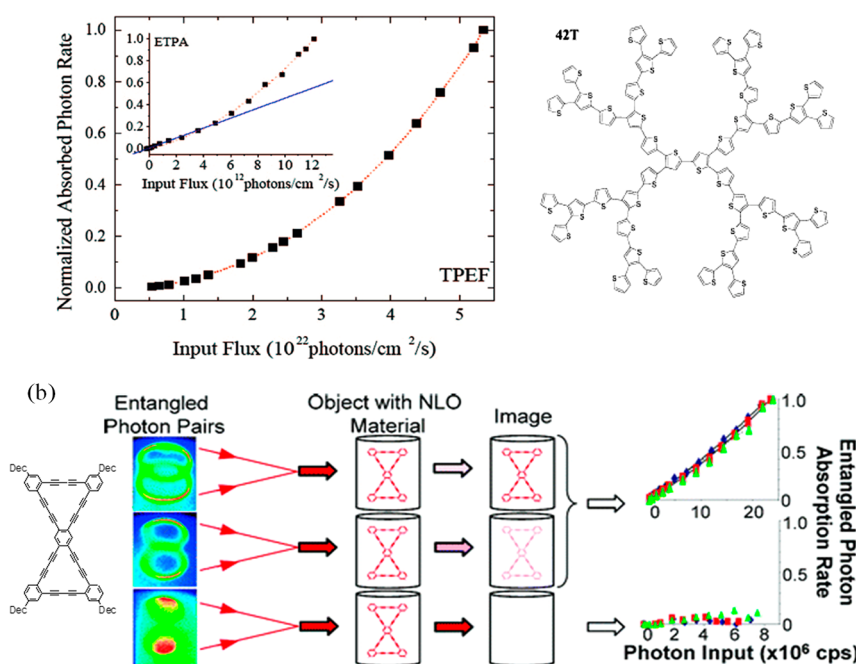


Figure 4. (a) Absorbed photon rate as a function of the input photon flux for the thiophene dendrimer. The two photon absorption rate is shown for both entangled light (insert) and random light, highlighting the difference in input flux used.²³ Reproduced with permission from ref 23. Copyright 2009 American Chemical Society. The structure of the thiophene dendrimer molecule under investigation is shown on the right. (b) Noncollinear, collinear, and separated spatial profiles of the spontaneous downconversion unit and corresponding dependence of ETPE rate as a function of the input flux are shown.³⁷ Results indicate a high ETPE rate for the collinear profile and no absorption for the separated pattern.³⁷ Molecule structure of the bis-annulene molecule is shown on the left. Reproduced with permission from ref 37. Copyright 2010 American Chemical Society.

system.¹ Dong-Ik Lee observed the linear ETPE rate as a function of intensity in an organic molecule for the first time. These pioneering results showed a large enhancement in the two-photon cross-section sensitivity, as an entangled photon flux of 10^6 – 10^7 photons/s was utilized to measure a large ETPE cross-section on the order of $\sim 10^{-17}$ cm²/molecule. This confirmed the possibility of conducting nonlinear spectroscopy on organic systems with very low intensity entangled photons. In the results (Figure 3c), which measure absorption via transmission methods, there is a clear linear dependence on the input flux at lower intensities, with a transition to quadratic (random) absorption dependence with increasing flux.¹ An exciting feature of the results was the ability to deduce varying ETPE rates at different entanglement delay times, confirming the nonmonotonic behavior of the ETPE cross-section due to the quantum interference of virtual states of the molecule with the entangled photon pair. Thus, it was shown that entangled states of light could be used to probe nonlinear optical transitions in molecules.

Following this experimental achievement, more work was done to determine the trends and comprehend the processes of ETPE in organic chromophores. In this vein, we conducted a systematic study on thiophene dendritic systems where the effect of increasing the dendrimer generation on classical (or random) TPA and ETPE was investigated.²³ This investigation was followed by a theoretical study of ETPE in thiophene dendrimers, providing a new insight on the quantitative relation between ETPE and the corresponding unentangled TPA based on the significantly different line widths associated with entangled and unentangled processes.⁵⁰ The difference between the radiative lifetime of the entangled and unentangled states plays a major role in making the ETPE

cross-section orders of magnitude larger than the TPA result. For both unentangled TPA and ETPE, the calculated cross sections were in good agreement with previously determined experimental values.^{21,50} The state-resolved analysis has been performed for dendritic molecules to unveil pathways for the ETPE processes, demonstrating changes in the interference behavior for different dendrimer generations.⁵⁰

Whereas ETPE is carried out with light intensities of $\sim 10^7$ photons/s, random TPA utilizes photon fluxes on the much higher order of $\sim 10^{20}$ photons/s, as depicted in Figure 4a. Despite these orders of magnitude difference in excitation flux, this study found that the dendrimer samples showed similar trends in cross sections with both random and entangled measurement methods, suggesting that both entangled and nonentangled light may probe similar states in these materials and that entangled light offers a quantum enhancement with increased sensitivity. The ETPE cross sections measured in this study were on the order of 10^{-18} cm²/molecule, which are comparable to previously measured values. Furthermore, like with random TPA, the ETPE cross sections increased with increasing dendrimer units, indicating that entangled photons are sensitive to the intermolecular interaction of thiophene dendrimer units. Another important assessment was determining the entanglement origin of the observed signal, which was achieved when we investigated the effect of the phase-matching conditions on ETPE.³⁷ Specifically, it was found that the ETPE signals of organic chromophores are dependent on the spatial orientation of the SPDC emission pattern (Figure 4b). The spatial indistinguishability between the signal and idler pair led to significant linear ETPE absorption rates, while there was no absorption at all observed when the photon pair are spatially distinguishable. It was apparent that the entangled

photon spatial properties affected the ETPA, which can be tuned by altering the characteristics of the photon pair.

The spatial correlation of SPDC photons, quantified by the entanglement area, A_e , is inherently linked to frequency entanglement through dispersion, since each frequency is subject to a unique propagation path defined by dispersion in the SPDC crystal.²⁹ ETPA scales as $\sigma_e \sim 1/T_e A_e$,²¹ and both T_e and A_e are defined by the SPDC frequency bandwidth, σ_f : $T_e \sim 1/\sigma_f$, $A_e \sim \sigma_f^2$ (degenerate type-I SPDC), and $A_e \sim \sigma_f$ (type-II SPDC). We found that the type-I σ_e increases linearly as σ_f decreases from 5 ps^{-1} to 0.1 ps^{-1} (T_e increases from $\sim 200 \text{ fs}$ to $\sim 10 \text{ ps}$) and can be within an order of magnitude of the linear absorption cross-section at the ETPA maximum ($T_e = 10 \text{ ps}$).³⁸ For type-II ETPA, σ_e is constant.³⁸ The maximum σ_e is more than 3 orders of magnitude larger than previous predictions for ps-scale T_e , where A_e was assumed constant even as σ_f (or T_e) changes (Figure 5). This result opens the

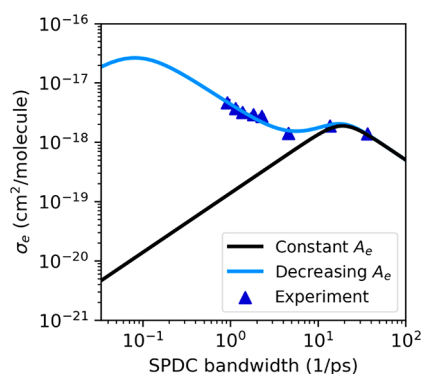


Figure 5. Type-I ETPA cross-section vs entangled photon bandwidth for the models where A_e decreases quadratically with the bandwidth (blue) and where A_e is constant (black). The blue triangles are experimental data. Reproduced with permission from ref 38. Copyright 2021 American Chemical Society.

door for measuring quantum dynamics and interferences on the ps-scale, such as in proton transfer, ligand binding/unbinding, isomerization, and water solvation.^{39–41} Chemists may also gain new control over reactions that require fs-ps intermediate steps, such as singlet–triplet energy transfer during the S_0 – T_n two-photon excitation in green fluorescent proteins.³⁹ The smaller A_e at ps T_e can also be used to improve the spatial resolution of ETPA microscopy by 3 orders of magnitude and possibly measure the size of structures within cells.

ETPA measurements have now been widely performed with different light generation methods and on different chromophores, yielding the signature linear absorption rate.^{36,42–45} ETPA has been conducted with continuous wave as well as femtosecond pulsed laser systems, has been verified to work with both type-I and type-II SPDC, and used to measure biological protein systems,³² and ETPA measurements have been taken via both single photon counts and coincidence counts (Figure 3d).⁴³ These studies have been successful in expanding our understanding of the ETPA process, how this is governed by the structure–function relationships of the chromophores, and the excitation pathways involved. In addition to experimental investigations, multiple theoretical studies have been conducted.^{24,46–49} A thorough computational analysis by Kang et al. corroborated the current experimental results, and ETPA cross sections of large organic

dendrimer systems were not only calculated but found to be in agreement with experimentally measured values.⁵⁰

4. ENTANGLED PHOTON EXCITED FLUORESCENCE

Great potential lies in the capability of using entangled photon pairs to induce and measure the fluorescence from the ETPA process. Fluorescence in general is highly favorable for spectroscopic measurements due to the lack of intrinsic background and the excellent signal-to-noise ratio it provides. Thus, experiments involving fluorescence such as two-photon excited fluorescence measurements, fluorescence lifetime imaging, and fluorescence microscopy have been integral to the optical spectroscopy of organic and biological materials. Furthermore, considering the quantum advantages of entangled photon pairs, classical fluorescence measurements could be enhanced with quantum light with low noise characteristics and low photon toxicity. For instance, the induced fluorescence from the ETPA process, that is, the excited two-photon entangled fluorescence (ETPEF), can be investigated and employed for different applications involving delicate materials. Like with classical excitation, ETPEF originates from a relaxed excited state, and the fluorescence detected is a measure of the state population created by the ETPA process.

The first report of fluorescence measurements in a molecule with entangled photon excitation was by our group in 2013.⁵¹ In this experiment, specialized equipment such as a fluorescence collection unit (FCU), screening to confine the experimental setup, and a CCD camera for the detection were used. Regarding the ETPA-induced fluorescence, it becomes increasingly difficult to determine whether one's experimental setup is deficient or the molecule under investigation does not show observable ETPEF. Therefore, it is important to understand what factors contribute to a molecule's ETPEF and how this pertains to different entangled photon sources.

We measured the ETPEF of three organic molecules namely bisannulene, zinc tetraphenylporphyrin (ZnTPP), and OM82C dendrimer with entangled light generated with a type-II BBO SPDC crystal, and the linear fluorescence signal was seen (Figure 6a).² This thorough study showed the linear ETPEF rates and conducted tests on how different entanglement parameters such as signal-idler delay and phase-matching spatial conditions affected the observed fluorescence intensity. A nonmonotonic dependence on the signal-idler delay was seen as well as an important dependence on the SPDC phase-matching conditions. Later, an ETPEF study investigated four similar thienoacene chain molecules.⁴² The ETPEF measurements of these compounds (Figure 6d) were also carried out using type-II SPDC. While the detected fluorescence was relatively weak (10s of fluorescence counts), these studies showed that ETPEF can be a useful tool in obtaining information about charge transfer and structure–function responses. An important aspect of these two investigations was that they showed the correlation between fluorescence intensity and the ETPA cross-section.^{2,42} Considering their fluorescence quantum yields, there is a clear correlation between the fluorescence intensity observed and the ETPA cross-section for the molecular systems measured in transmission experiments in both studies, which confirms the ETPA origin of the observed signal.

Type-II SPDC has not been the only photon pair generation method for successful ETPEF measurements. In 2021, Tabakaev et al. utilized periodically poled type-0 SPDC with

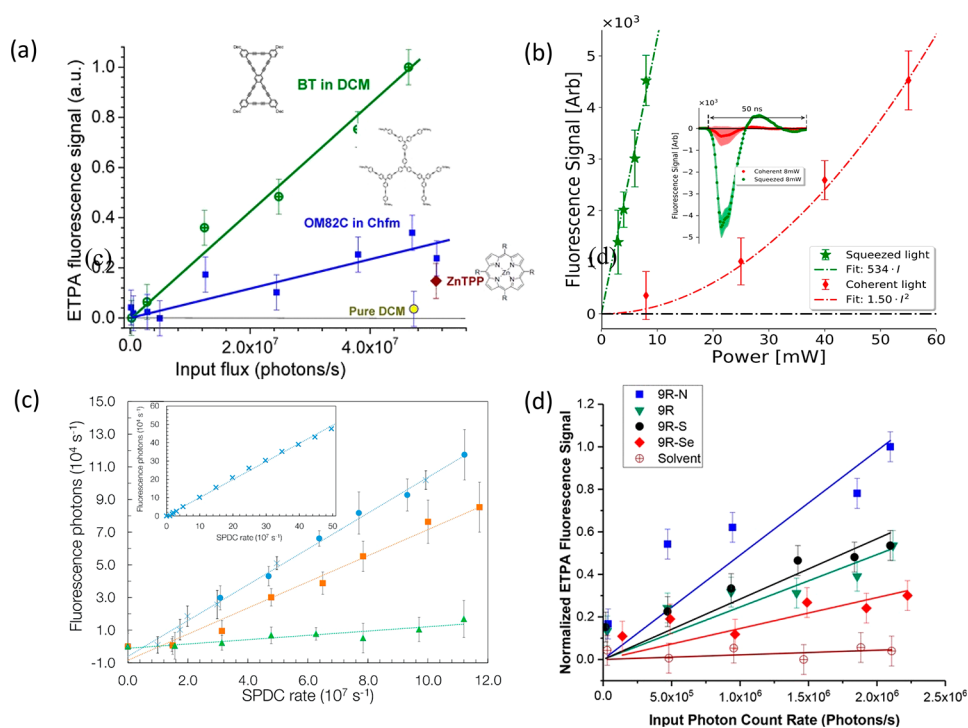


Figure 6. Fluorescence induced by entangled photon pairs. (a) ETPEF from type-II SPDC in organic molecules.² Reproduced with permission from ref 2. Copyright 2017 American Chemical Society. (b) Fluorescence induced by squeezed light and uncorrelated light in Fluorescein.⁵² Reproduced with permission from ref 52. Copyright 2020 American Institute of Physics. (c) ETPEF of Rhodamine 6G excited with type-0 SPDC photon pairs.⁵³ Reproduced with permission from ref 53. Copyright 2021 American Institute of Physics. (d) ETPEF of thienoacene molecules.⁴² Reproduced with permission from ref 42. Copyright 2018 American Chemical Society.

a higher flux of 10^8 photons/s, for ETPEF in a rhodamine 6G molecule, and a linear dependence on photon flux was obtained (Figure 6c).⁵³ The comparatively small magnitude of cross sections measured ($\sim 10^{-21}$ cm²/molecule) suggests that it may be easier to observe fluorescence of molecules with lower cross sections by using a higher photon flux. Again, this study thoroughly tests the entanglement origin of the observed fluorescence signal by incorporating measurements with different interphoton delay times, different phase-matching conditions, and background measurements with no illumination and with solvent only. In another investigation by Agarwal and co-workers, ETPEF was also observed with squeezed light at higher intensities ranging from 10^{13} to 10^{16} photons/s.⁵² While higher powers of squeezed light resulted in nonlinear behavior of ETPEF, at lower intensities, the characteristic linear dependence on photon flux was indeed seen for DCM.⁵² For Fluorescein, there was clear linear behavior of the ETPEF signal throughout (Figure 6b). Different types of quantum light generation can be utilized toward fluorescence measurements, which can lead to different results.

The detuning energy is a key factor to the ETPEF process, and this, based on the molecule's electronic states, often determines whether ETPEF can be observed for the molecule. In some cases, ETPEF has been clearly observed, whereas in other molecules, where there is bright classical TPEF, there is no observed ETPEF. This is dependent on the detuning energy, dipole moments, and the subsequent pathway used for ETPEF for a given molecule's transitions.^{48,54} In the virtual transition pathway, the intermediate states close to resonance with the entangled photons leads to a strong interaction between the molecule's states and the entangled photons. This could cause an enhancement in the ETPEF signal, and

fluorescence is observed. On the other hand, molecules with larger detuning energies do not experience this interaction enhancement, and ETPEF becomes less likely to be seen. This phenomenon of measuring classical signals for a molecule but no entangled signals has been observed for a stilbene derivative as well as branched alkene and alkyne chromophores.⁵¹ The molecular parameters, coupled with the photon pair properties and experimental setup, are all factors that play a role in the ability to observe and measure entangled light excited fluorescence signals. The very low fluorescent light detected as a result of entangled photon excitation is still a challenging process, and many experimental parameters can affect the results.^{55–57} These contributions must be further characterized to accelerate exciting applications of quantum light fluorescence microscopy and imaging.

5. IMAGING WITH CORRELATED PHOTONS

Among the applications of nonclassical states of light, microscopy is essential in broad areas of science from physics to biology.^{3,58–60} Using nonclassical states of light can open possibilities of realizing low-intensity microscopy at intensity levels not achievable with classical resources.^{3,58,59} Using quantum states of light for illumination, precise phase and linear absorption measurements in a microscopic format have been previously reported, and precision beyond the standard quantum limit has been achieved in a microscope.^{58–61} A significant improvement in the signal-to-noise ratio up to 35% utilizing quantum enhancement has been achieved.⁶⁰ Another approach toward entangled photon microscopy utilizes the enhanced multiphoton absorption of the entangled photons. This method was theoretically proposed more than two decades ago,⁶² but we only recently demonstrated it

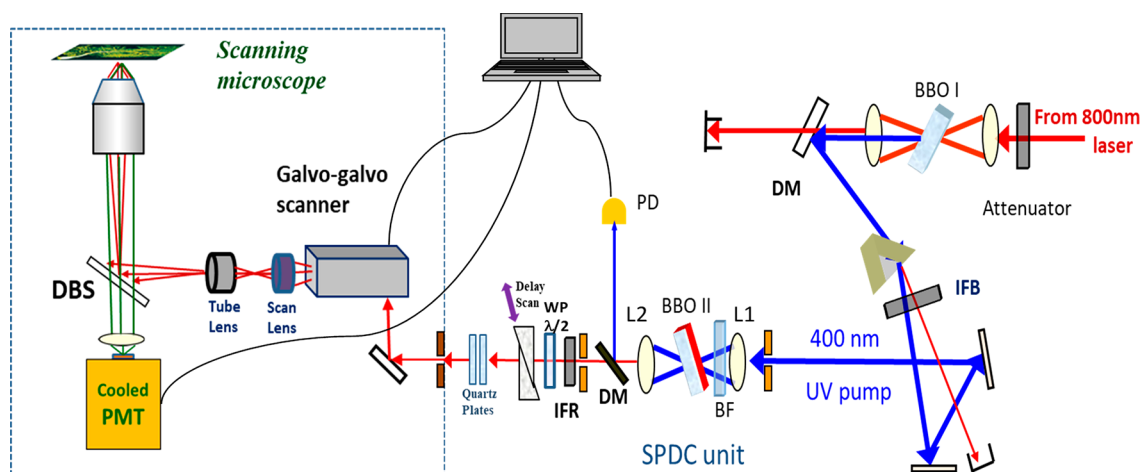


Figure 7. ETPEF scanning microscope optical diagram. Interference filters (IFB, IFR) and dichroic mirrors (DM) separate second harmonic (SH) light from fundamental and entangled photons from SH. Pump power references are provided by photodetector (PD). A variable delay between the down-converted photon pair is accomplished with the optical delay unit consisting of the $\lambda/2$ wave plate (WP), crystal quartz wedges on a delay stage, and crystal quartz plates. The biphoton beam undergoes raster scanning in the microscope galvo-galvo scanner. The dichroic beam splitter (DBS) directs the excitation beam to the objective lens. The fluorescent signal from the sample was epi-collected by the microscope objective lens and detected by the cooled PMT.³ Reproduced with permission from ref 3. Copyright 2020 American Chemical Society.

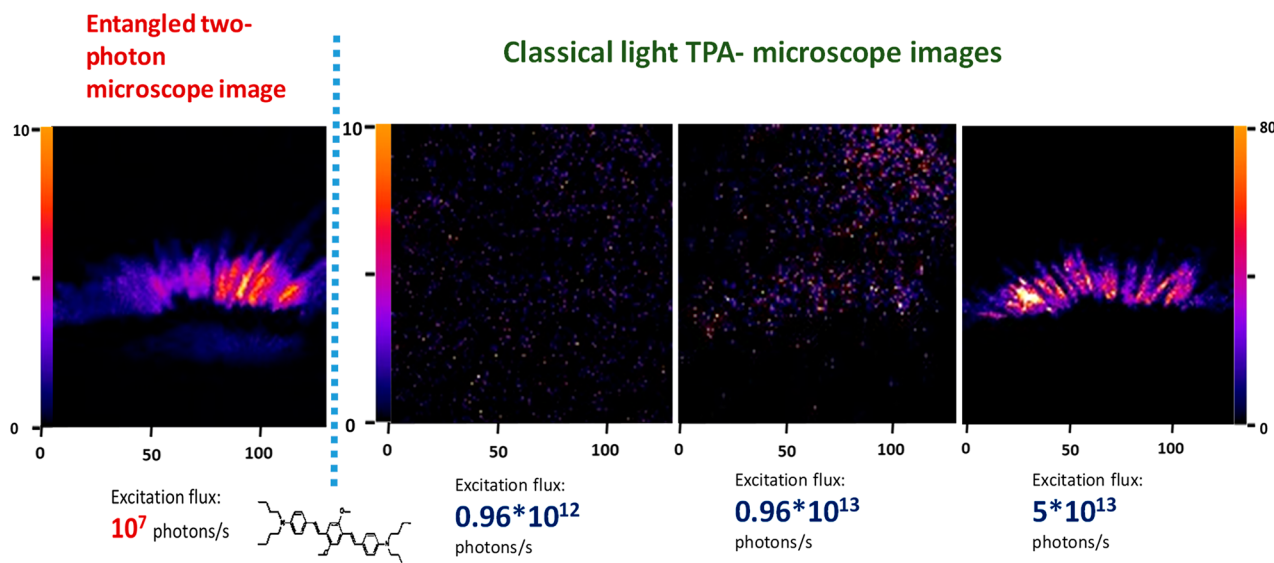


Figure 8. Scanning microscope image obtained with entangled photon excitation (left) in comparison with classical light two-photon excitation at different excitation fluxes. Excitation flux (average) is shown under respective microscope images. Sample: Drop cast film of bis(styryl)benzene derivative (Bu_2/OMe). Color bar intensity scales are given in numbers of fluorescence photons per pixel. Spatial scale is indicated in pixels at the bottom of each image.³ Reproduced with permission from ref 3. Copyright 2020 American Chemical Society.

experimentally in organic thin films,³ suggesting the potential to utilize the ETPE effect for fluorescence microscopy. Our scanning microscope was based on detecting fluorescence selectively excited by entangled photons produced by type-II SPDC (Figure 7).^{52,63,64,3}

The SPDC unit was able to produce 1.2×10^7 photons/s output flux (singles) and a signal-idler coincidence rate up to 1.5×10^6 coincidence counts/s.³ A polarization-dependent optical delay line based on birefringent material wedges was inserted between the SPDC and the microscope input.³ This delay system allowed for the investigation of microscope images as a function of the interphoton delay at times comparable with the entanglement time $T_e = 63$ fs.³ Utilizing the scanning microscope with the sample illuminated by the SPDC entangled photon beam, we were able to obtain images

of a number of organic thin-film samples as well as the biologically important flavin mononucleotide⁶³ and nicotinamide adenine dinucleotide⁶⁴ which are endogenous signatures of cells.^{63,64} In the entangled photon microscope experiments, the actual background with the laser pump blocked was around 0.3–1 photons per pixel (128×128 pixels) depending on the number of frames (1000–2000) and microscope alignment conditions.³ The ETPE-induced microscope images obtained were compared with those collected under weak classical two-photon excitation at 800 nm for reference (Figure 8).⁴² For classical 800 nm two-photon measurements, the fundamental coherent laser beam from the femtosecond laser was adjusted to an average flux level of 10^{13} – 10^{15} photons/s (submilliwatt range) in order to produce about the same fluorescence intensity detected with the much weaker entangled photon

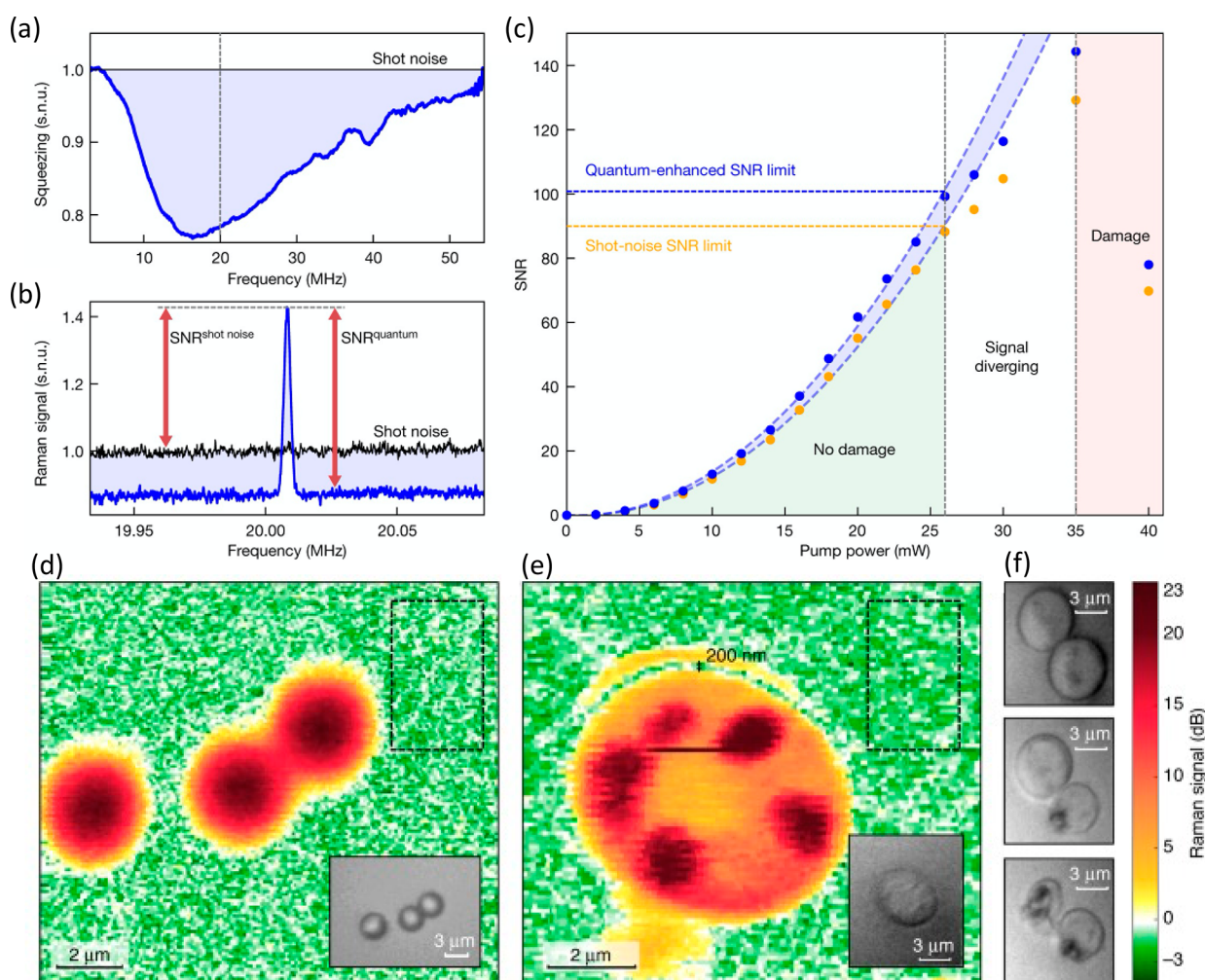


Figure 9. (a) Noise spectrum of squeezed light normalized to shot noises. Maximum squeezing attained near the Raman modulation frequency of 20 MHz (dashed line). (b) Stimulated Raman signal of a polystyrene bead showing reduced noise below the shot noise with squeezed Stokes light. (c) Graph showing signal-to-noise ratio vs pump power for a polystyrene bead. (d) Images of polystyrene beads and (e) a live yeast cell taken with the quantum coherent microscope. Green colored background has no Raman signal, and the noise is measured in these portions (indicated with dashed boxes). The insets are bright-field microscopy images and (f) shows the photodamage with high pump intensities. Reproduced with permission from ref 60. Copyright 2021 Nature.

excitation. The image obtained with classical light via random two-photon absorption was then compared with the image produced by the entangled photon pairs from the SPDC unit (Figure 8).

The experiments showed that the classical light flux of $\sim 10^{13}$ photons/s created an image of the same intensity (in photons/pixel) as that obtained with entangled photon light with an average photon flux of $\sim 10^7$ photons/s.³ This result demonstrates a substantial enhancement of the two-photon absorption efficiency (6 orders of magnitude) when going from classical (random) two-photon absorption to the absorption of highly correlated entangled photon pairs in the microscope configuration.³ Additionally, experiments demonstrating the image dependence on the delay between two components of the entangled photon pair were performed.³ These experiments showed a nonmonotonic dependence of the image on the intercomponent delay stemming from the quantum interference effects.^{20,21,37,57} These quantum interference effects are specific to ETPA and are not observable with classical light.^{1,2,21,24,48,51,65} The observation of the quantum interference effects in the microscope is a strong indication of the entangled photon origin of the image.³

Overcoming photodamage with quantum correlations is not limited to two-photon excitation, and Bowen and colleagues recently demonstrated this with a highly selective coherent Raman microscope.⁶⁰ In their experiment, they observed an impressive 35% improved signal-to-noise ratio, compared to conventional classical light microscopy. This is in accordance with a 14% improvement in concentration sensitivity, reducing high phototoxicity and allowing for better resolution of otherwise unobservable biological structures. The Raman microscope was set up to perform highly specific measurements to prove the vibrational spectra of biomolecules. The quantum light eases the photon budget, increasing signal-to-noise ratio as Raman scattering can be observed with even less than a single photon within the measurement time frame. Quantum enhanced images of samples of both dry polystyrene beads and living *Saccharomyces cerevisiae* yeast were obtained (Figure 9), with 23 to 35% enhanced signal-to-noise ratio leading to increased image contrast.⁶⁰ As such, they were able to view features that were uncovered below the shot noise limit.

It has also been theoretically proposed and simulated that quantum light correlations might enhance the Raman signals

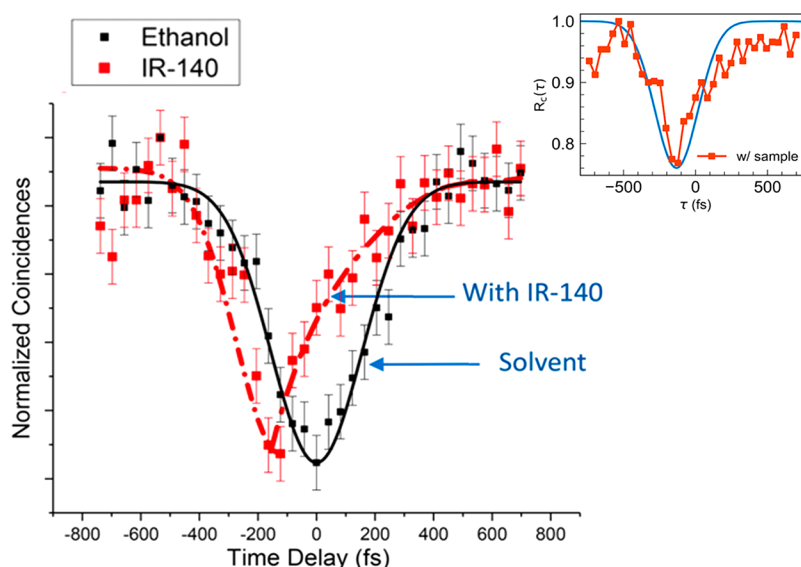


Figure 10. HOM dip with (red) and without (black) sample in the interferometer path. Inset: Data with sample computationally fitted. Reproduced with permission from ref 4. Copyright 2021 American Chemical Society.

and their signal-to-noise ratio.^{66,67} Another theoretical approach considered using a classical laser pulse excitation followed by the interaction with one of the photons of the entangled pair. The second entangled photon does not interact with the sample but is used for coincidence counting with the first photon. This interaction scheme could provide a unique temporal and spectral window which is helpful for the resolution of fast photodynamics in a way that is not possible with only classical pump–probe techniques.⁶⁸

6. QUANTUM INTERFEROMETRY FOR ULTRAFAST MOLECULAR SPECTROSCOPY

What if in addition to entangled photon spectroscopy being used to linearize two-photon absorption, it could also be utilized to study how entangled photon–molecular interactions modify the inherent correlations of the quantum light, and determine information about the molecular excitation? This question has been tackled with increasing vigor on the theoretical front, with studies on interferometric schemes where entangled light–matter interactions change the quantum field and its statistics, offering insights into matter information.^{69–72} The nonlocal nature of entangled light in two-photon interferometry is already exploited in metrology,⁷³ and it is proposed that upon interfering quantum states of light with molecules, complex coincidence signals could be obtained to provide material information.⁷ While the concept has been proposed, adequate theoretical tools to analyze experimental results are needed. Models that connect the physics and chemistry to the experiment in terms of matter and field correlation functions must be developed, and the vast possibilities involving quantum interferometry for spectroscopy will become realities.

Mukamel et al. have been instrumental in proposing theoretical outlooks involving spectroscopic entangled photon interferometry. One of these proposals involves a novel femtosecond stimulated Raman spectroscopy technique where the enhanced control of entangled photons and their independent temporal and spectral characteristics can resolve the overlapping features of ordinary congested classic spectra.⁶⁹ Other proposals from Mukamel and other

researchers include interferometric signals for pathway selectivity,⁷⁰ multidimensional spectroscopy that may suppress uncorrelated background signals,⁷⁴ and interferometric TPA techniques with a triphoton entangled state with stronger spectrally dispersed photon-counting signals than a typical biphoton state.⁷¹

The backbone of these proposed techniques is two-photon interferometry which is best described with a Hong–Ou–Mandel (HOM) interferometer.⁷⁵ In an HOM interferometer, the entangled photon pair are separated and a time delay introduced between them via differences in their propagation paths. After this temporal compensation, the photons meet and interfere at a 50:50 beamsplitter, where single photon detectors measure whether the photons emerge from the same or opposite sides of the beamsplitter. The indistinguishability of the photon pair lead to destructive interference of the indistinguishable paths and a subsequent drop in the coincidence counts known as the “HOM dip”. Any factor that distinguishes the photon pair affects the width and amplitude of the observed dip. Thus, the dip carries any matter interactions the entangled photons encountered, making this a promising outlet for spectroscopic measurements. The increased sensitivity of quantum interferometers^{76,77} can improve the accuracy of our measurements of material linear and nonlinear susceptibilities. Experimentally this scheme was first demonstrated in solid-state crystals and nanostructures with relatively narrow absorption lines.⁸⁰ The authors obtained information about coherent dynamics and dephasing processes in these systems. The same formalism was applied to a separate computational work studying the entanglement between light and the microscopic quantum states of a sample.⁷⁸

A big question that we answered was whether a quantum interferometer could resolve signatures from thin sensitive organic samples. An HOM signal is indeed sensitive to a resonant organic sample present in its path, as was confirmed in our recent experimental and theoretical study.⁴ What was increasingly important was developing a theoretical framework that could analyze experimental spectra. The coincidence counting rate of an HOM setup that has experienced a linear

spectroscopic interaction can be described by the following equation:⁴

$$R_c(\tau) = A \left(\frac{1}{2} - \frac{1}{2} \iint d\omega d\omega' f \times (\omega', \omega) T \times (\omega') T(\omega) e^{i(\omega - \omega')\tau} \right)$$

where $f(\omega', \omega)$ denotes the amplitude of a two-photon wave function, and $T(\omega)$ is a transition amplitude of the matter under study that contains the matter susceptibility. Evidently, the matter interaction experienced in one arm is encoded in the transmitted field, presenting as an alteration in the shape and a shift of the HOM dip. This change in shape and shift of the dip were shown theoretically (Figure 10 inset) and verified experimentally (Figure 10).⁴ Such an experiment can be employed to measure time-resolved properties, as was successfully carried out in this investigation. The dephasing time of an IR-140 chromophore of 102 fs was measured with femtosecond precision with the fitting of the experimental data (Figure 10, inset).⁴ Moreover, studies have shown that this can be expanded to more complex nonlinear spectroscopic investigations.⁷⁹ For instance, an external classical laser pulse can create an excited state in a material placed in an HOM interferometer, which can then be probed with entangled photons. The nonlinear optical signals will be observed in the coincidence counts with better sensitivity, low flux, and the control parameters offered by entangled photons.

7. OUTLOOK

From the early beginning of the generation of squeezed states of light to the first entangled nonlinear optical measurements to the illustrations of entangled light enhanced microscopy, there has been great progress in the development of the ideas and approaches of this area of research. While many great challenges remain in the more general and practical use of quantum light for sensing and imaging, the important scientific and technological uses are clear. The future is bright for this and related areas of research in relationship to chemistry. Applying new tools and “control knobs” to the understanding of electronic states is critical to our ability to expand our understanding of light-driven chemical processes. The future opportunity to enhance electron and energy transfer processes with quantum light as well as absorption of very weak signals resulting from virtual state interactions are exciting prospects for chemists. The next steps in our journey with quantum light are to provide new structure–function relationships for novel molecular systems, enhance the generation of entangled or quantum light with established or new methods, and provide further light–matter interactions with biological and tissue related systems. This is an exciting time for the use of nonclassical light in chemistry.

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Notes

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