Recent Advances of Pure Organic Room Temperature Phosphorescence Materials for Biomedical Applications

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Organic room temperature phosphorescence materials have a wide range of applications in organic electronics, chemical and biological sensing, and photo-theronostics owing to the triplet state population and long lifetime. Phosphorescence from organic molecules is highly attractive since they are abundant, cost effective, easily processable, stable and biocompatible. However, for efficient phosphorescence to realize, efficient intersystem crossing (ISC) of excited electrons to triplet state is required, which could be easily achieved in organometallic compounds where charge transfer between metal and ligand facilitate the ISC. Organic compounds are rarely phosphorescent in nature because the emission from the triplet excited state is non-radiative due to some detrimental processes, such as thermal perturbations, intramolecular motions, and intermolecular interactions with oxygen and humidity. Major efforts are being made to achieve simultaneously long life time and high quantum yield from organic materials,resulting the emergence of a number of strategies and organic materials. The evolved materials have been utilised for bioimaging, photodynamic therapy and photothermal therapy. This review discusses the constraints in developing the organic room temperature phosphorescence materials, summarizes the very recent advancements reported in 2021 and provides the future prospects.

Keywords: *Room temperature phosphorescence, Organic materials, Supramolecular assembly, Polymer encapsulation,Photo-theronostics.*

Introduction:

The evolution of life on earth was impossible without the light, which is an everyday experience and we often understand the importance of light by its absence. Currently light based technologies are being promoted to find solutions to global challenges in health, energy, and agriculture.[1] Emission of light from molecules and materials occurring due to the radiative decay between electronic states of different spin multiplicity is called phosphorescence, which is a spin forbidden process (Figure 1).[2] For efficient phosphorescence to realize, efficient intersystem crossing (ISC) of excited electrons are required, which could be easily achieved in organometallic

compounds where charge transfer between metal and ligand facilitate the ISC. Organic compounds are rarely phosphorescent in nature because the emission from the triplet excited state is non-radiative due to some detrimental processes, such as thermal perturbations, intramolecular motions, and intermolecular interactions with oxygen and humidity.[3] Moreover, the electrons in the organic compounds are tightly bonded, which inhibit efficient ISC.[4] Phosphorescence materials have wide range of applications in different areas owing to their high electroluminescence efficiency.[5] They are utilized in organic electronics, chemical and biological sensing as well as in bioimaging.[6] Phosphorescence from organic molecules is highly desirable since they are highly abundant, cost effective, easily processable, stable and biocompatible.[7] Therefore, huge effort has been invested to realize efficient room temperature phosphorescence (RTP) from organic molecules, resulting a large number of publications reporting different strategies and new chromophores exhibiting RTP.[8] These strategies mainly address the two main issues of organic RTP: 1) efficient ISC to enhance triplet state population; 2) rigidification to restrict the molecular motion for preventing non-radiative decay from triplet state.[9] To enhance triplet state population introduction of halogen bonding,[10] BF_2-chelates,[11] triazine,[12] sulfone,[13]arylboronate ester,[14]siloxy group,[15]thiocarbonyl group,[16]triphenyl phosphene,[17] polyimides,[18]polynuclear aromatic systems[19] were utilized. To reduce non-radiative decay via molecular motion several strategies including polymer assistance ,[20]crystallization,[21]supramolecular gel formation,[22] and metal-organic framework coordination[23] were used. We have recently developed halogen bond induced room temperature phosphorescence from capped gamma amino acid at crystalline state.[24]A halogen bond (R–X···Y–Z) is realized when a net attractive interaction operates between an electrophilic region associated with a halogen atom in a molecular entity, and a nucleophilic region in another, or the same molecular entity.[25]

Despite these great advances two important areas remain relatively unexplored in this field, which are: 1) development of organic RTP material at amorphous state, and 2) organic phosphorescence at air equilibrated solution. These requirements are highly important to find applications of RTP in biological settings. Except the crystallization in above mentioned strategies, additional molecules and matrices are required in the rigidification methods, which add complexity to their applications with reduced performance due to the diluted organic RTP molecule concentration. This is particularly a limitation in biological application as the biocompatibility and negligible interference between the matrix and biosystem should be maintained.[6] Moreover, crystallization which required special conditions to achieve for phosporescence has also limited scope in biological applications.

Organic room temperature phosphorescence materials exhibit great potential in biomedical applicationsbecause of its inherentadvantage of long emission lifetime. The conventional bioimagingprocess dependson fluorescence signals acquired on real-time light excitation.In these processesautofluorescence from biomolecules interfere with desired signals.[26] Therefore, exploitation of long-lived RTP materials for bioimagingapplications via time-resolved imaging techniques is advantageous to minimize or sometimes eradicate the background signals from autofluorescence with higher signal-to-noise (S/R) ratios, which in turn improve the sensitivity.[27-28]Low toxicity,ease of modification by molecular engineering, low cost and biocompatibility makes the organic RTP materials suitable forapplications in the biomedical field.

This review focuses on the very recent developments on the applications of the organic phosphorescent materials (reported in 2021 and not included in any previous review) in the fields ofbioimaging, photodynamic therapy (PDT) and cancer theronostics. Photodynamic therapy utilizes triplet state generating photosensitizers, which upon irradiation of light sources, generates reactive oxygen species (converting triplet oxygen to singlet oxygen) by energy transfer from the radiative decay from triplet state to singlet state and thereby induces cell apoptosis and death. Several review

articles had summarized the biological applications of the organic phosphorescent materials.[29-35] Since the field is very rapidly growing, a timely up to date review will be a valuable contribution to the field. Organic supramolecular assemblies, polymer supported organic nano-materials and aggregationinduced emissive materials will be discussed in this review. Finally, constraints of applications of organic phosphorescent materials in biological applications and the future prospects will be discussed.

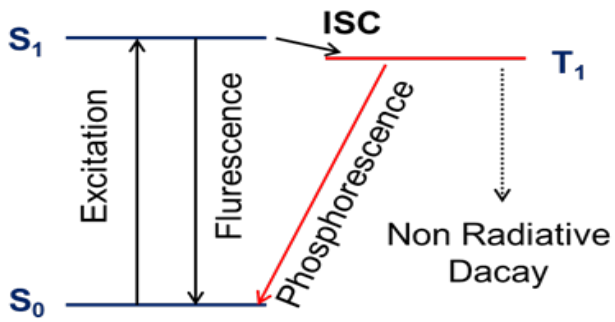

Figure 1: Schematic Jablonski diagram of photoluminescence for room temperature phosphorescence materials.

Supramolecular assembly:

To provide the rigid environment around the chromophore for realizing RTP supramolecular host-guest assembly has been explored. For this purpose, macrocyclic hosts containing hydrophobic cavities such as cyclodextrins (CDs)[36] and cucurbiturils (CBs)[37] were used. They interact with the guest molecules through non-covalent interactions such as electrostatic interactions, hydrogen bonding, hydrophobicinteractionsand so on.There are several advantages of using these macrocyclic hosts to achieve RTP.They provide rigid environment for guest molecules through stable host–guest complexation and thereby inhibits non-radiative transitions. Moreover, the hydrophobic cavities can protect phosphorescent molecules from quenching by water or oxygen.

Liu and co-workers[38] had covalently attached an ORTP moiety (4-(4-bromophenyl)-pyridine) with β-cyclodextrin followed by encapsulation of the modified 4-(4-bromophenyl)-pyridine within cucurbit[8]uril (CB[8]) in a 2:1 ratio (Figure 2). This supramolecular assembly produced efficient RTP in aqueous solution at 510 nm with phosphorescence lifetime 504 μs. The phosphorescence emission energy was further transferred to excite rhodamine B which encapsulated into β-cyclodextrin. Phosphorescence energy transfer leads to delayed fluorescence having emission maxima at 590 nm. The strong binding affinity between β-cyclodextrin and adamantine was exploited to construct higher order supramolecular assembly by encapsulating hyaluronic acid modifiedadamantane. Hyaluronic acid is known to target cancer cells by specific binding with CD44 and RHAMM receptors. Thus an efficient solution state light harvesting supramolecular assembly with cancer cell targeting ability was developed. The system, CD-PY@CB[8]@RhB@HA-ADA, was successfully employed for mitochondria targeted imaging of human lung adenocarcinoma cells (A549 cells) (Figure 2).

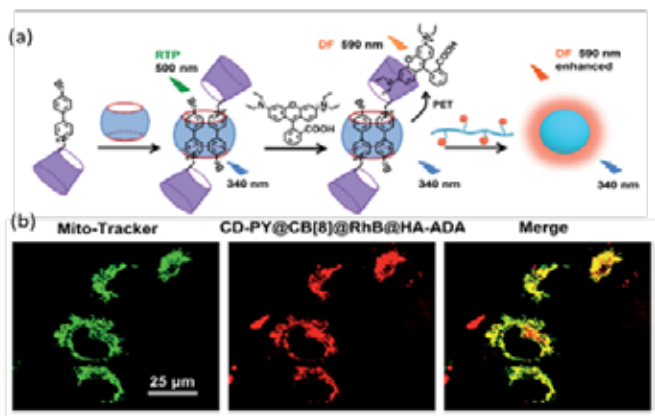

Figure 2: (A) Schematic of the formation of nanoparticles obtained for supramolecular host guest assembly. (B) Mitochondria targeted imaging of human lung adenocarcinoma cells using the supramolecularnanoparticles.

Polymer Supported Organic Nanomaterials:

Development of organic room temperature phosphorescent materials exhibiting high quantum yield and long life time at the same time is very challenging. Tang, Li and co-workers[39] have recently reported a strategy to overcome this shortcomings by mixing guest and a host molecule together in 100:1

ratio to form nanocrystals (M-CH_3 and M-C_2H_5) (Figure 3). Phenothiazine derivatives (N-methylated or ethylated) were used as guest and corresponding phenothiazine dioxide derivatives were selected as host. Phosphorescence efficiency was achieved as high as43% and lifetime was achieved as high as 25 minutes in aqueous solution. The RTP nanomaterials for biological applications were achieved by encapsulating the host-guest nanocrystals in biocompatible amphiphilic co-polymer PEG-b-PPG-b-PEG. The hydrophilic PEG chains solubilize and protect the nanocrystals in aqueous medium. The polymer coated nanocrystals were utilized for subcutaneous imaging, lymph node imaging and thermal printing applications. The formation of triplet exciplex between donor and acceptor moieties was the mechanism behind the improved phosphorescence efficiency.

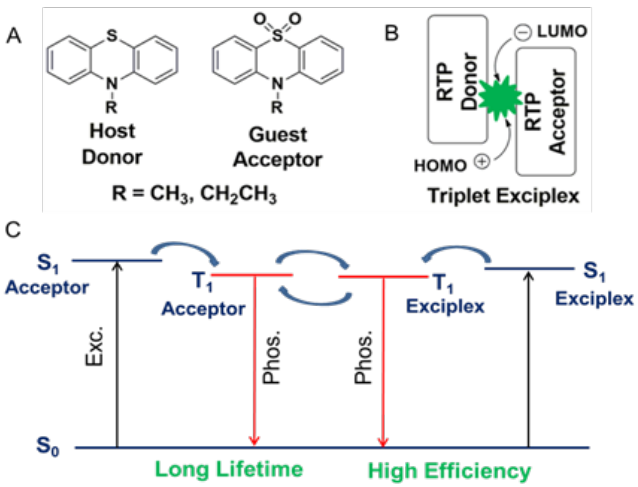

Figure 3: (A) Structures of the host and guest molecules. (B) Triplet exciplex formation as internal mechanism of the highly efficient phosphorescence quantum yield and long lifetime.

An and co-workers[40] have reported ultra-long organic room temperature phosphorescence in solution state from nanoparticles obtained from 9.9'-(2,5-Dibromo-1,4-phenylene)bis[9H-carbazole] upon encapsulated in amphiphilic surfactant polyvinylpyrrolidone (PVP) polymer (PDBCz@ PVPanoparticles) (Figure 4A). The phosphorescence lifetime of the PDBCz@PVPnanoparticles was 284.59 ms and quantum efficiency was 7.6%. The efficient phosphorescence properties were exploited for thelow costfluorescence interference free bioimaging in living cells and zebrafish. The simultaneous effects of carbazole and heavy atom effect of bromine contribute majorly to the improved phosphorescence properties. The encapsulation into surfactant polymer matrix helps to the water solubility of hydrophobic organic nanoparticles and provides the required rigidification for efficient phosphorescence in solution.

Ding and co-workers[41] have developed efficient RTP materials by regulation of molecular aggregation of a series of carbazole containing catbonyl derivatives (4-(9H-carbazol-9-yl) benzaldehyde (CBA))(Figure 4B) with different alkyl substituents. Longer lifetime up to 868 ms and higher efficiency of 51.59% were obtained. Heavy mechanical grinding leads to bright RTP intensities indicating robustness of the RTP features. Phosphorescent nanoparticles were prepared by using biocompatible amphiphilic copolymer PEG-b-PPG-b-PEG as encapsulating matrix. The nanoparticles were used for time-resolved phosphorescence imaging oflymph node in a live mouse and orthotopic lung tumor imaging with a high signal-to-background ratio. The phosphorescent compounds were also used for advanced security encryption.

Kapurand co-workers[42] exploited the tunable fluorescence and phosphophorescenec properties of iodine substituted difluoroboron β-diketonates(Figure 4C) for the sensing of oxygen which was used for intracellular neuronal imaging. Difluoroboron β-diketonate was covalently attached to poly (lactic acid) and thereby nanosensors were prepared. The difluoroboron β-diketonate linked poly (lactic acid) nanoparticles nanopartilces were previously reported for tumor hypoxia imaging. The nanoparticles were dualemissivehavingoxygen-insensitive fluorescence and oxygen-sensitive phosphorescence which enabled real-time ratiometric oxygen sensing with spatial and temporal resolution.The nanoparticles were applied in mouse brain slices to investigate oxygen distributions and neuronal activity.Study of oxygen maping in

living brain slices revealed that oxygen was found to be mostly consumed by mitochondria near synapses. The difluoroboron β-diketonate linked poly (lactic acid) nanoparticles exhibited excellent response when the conditions varied from normoxic to hypoxic and when the neuronal activity was increased by increasing K^+concentration.

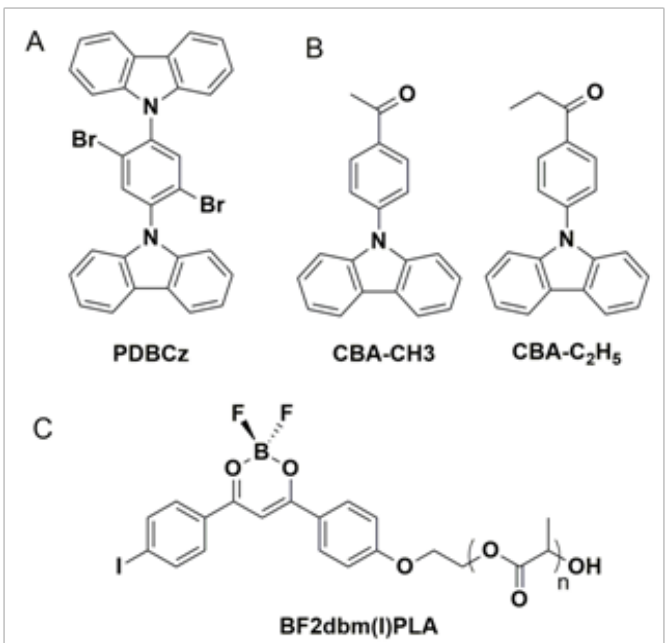

Figure 4: (A) Structure of 9.9'-(2,5-Dibromo-1,4-phenylene) bis[9H-carbazole] (PDBCz) reported by An *et.al.* (B) Structures of different alkyl substituted 4-(9H-carbazol-9-yl) benzaldehydes (CBA) reported by Ding *et.al.* (C) Structure of iodine substituted difluoroboron β-diketonates attached to poly (lactic acid) reported by Kapur*et.al.*

Aggregation induced emissive materials for theronostics:

The ronostics implies the combination of therapeutics and diagnostics. Cancer phototheronostics involves the detection and treatment of cancer by using light based technologies including bioimaging, photoacoustic imaging, photothermal imaging, photodynamic therapy and photothermal therapy. Phototheranosticsis a promising direction for modern precision medicine for treatment of cancer, as it has the advantages of time gated diagnosis with high sensitivity and simultaneous in situ therapy. The strategy can achieve excellent spatiotemporal precision and minimal toxicity to normal tissues under photon irradiation. Zhao and co-workers[43] have recently developed a one-for-all phototheronostic agent based on aggregation induced emission properties of DPMD and TPMD molecules having cross shaped donor acceptor structure (Figure 5).The compound TPMD having high donor–acceptor (D–A) strength, small singlet–triplet energy gap, andabundant intramolecular rotators and vibrators was an ideal candidate for the theronostic applications. Biocampatible nanoparticles were prepared from TPMD after encapsulating into amphiphilicpolymer F127. The TPMD NPs possess adequate near-infrared (NIR) fluorescence emission at 821 nm which was used for fluorescence imaging. It produces effective reactive oxygen species, which was utilized for photodynamic therapy (PDT)*in vivo*, in mouse. The outstanding photothermal effects were exploted for photoacoustic imaging, photothermal imaging, and photothermal therapy (PTT). The nanoparticles exhibit excellent biocompatibility and biosafety which make them effective for cancer treatment.

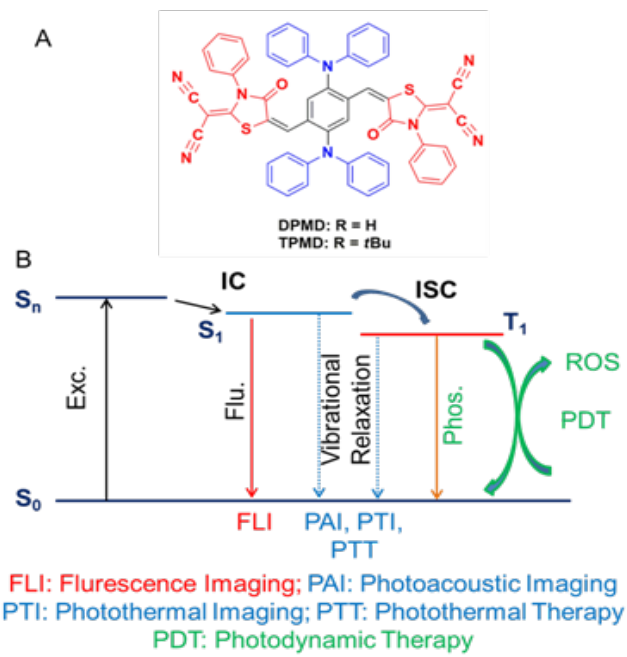

Figure 5: (A) Structures of the AIEgensDPMD and TPMD reported by Zhao *et.al.* (B) Schematic of the Jablonskidiagram related to different imaging and therapeutic technologies.

Summary and Outlook:

This review summarized the very recent progresses in the field of the use of organic room temperature phosphorescence materials in biomedical applications. Thevery rapidly growing area of research has fosteredfew strategies to achieve the long lifetime and high quantum yield from organic building blocks simultaneously. Therefore, attention should be paid to the development of efficient design to achieve inherent high quantum yield and long lifetime together which are essential for biomedical applications. The application of ORTP materials in biological application is still in infancy. Majorly, amphiphilic polymer matrices have been utilized to provide the required rigidification to achieve the ORTP in biological settings. However, polymers may have negative effect on health when used in biomedical applications. Encapsulation of the organic luminophores in polymer matrix may dilute the concentration of the photo-active compound. Therefore, alternative strategies involving the fabrication of self-assembling nanoparticles of organic phosphorescent building blocks which will lead to efficient ORTP in aqueous medium.Moreover, development of room temperature phosphorescence materials that can be excited by visible or even NIR light is necessary. The advantage of NIR light is that it can penetrate biological tissues deeper than UV lightwhich reduces the tissue scattering and minimizes the background autofluorescence. Importantly, it is essential to increase the lifetime of phosphorescence materials to minutes and even hours which will have practical biomedicinal applications.

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