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Functional Organic Nanocrystals

Koichi Baba¹, Hitoshi Kasai^{2,3}, Kohji Nishida¹ and Hachiro Nakanishi²

¹*Osaka University*

²*Tohoku University*

³*PRESTO, Japan Science and Technology Agency
Japan*

1. Introduction

The topic in this chapter concerns organic nanocrystals. Numerous scientific researches of nanocrystals are focusing on inorganic compounds such as a metal and a semiconductor. The research related to organic nanocrystals is relatively new compared to that of inorganic nanocrystals. Nearly two decades ago, our research team had developed a novel preparation method of organic nanocrystals, what we call the reprecipitation method. Since then, we have been leading the research area of organic nanocrystals. The reprecipitation method has bottom-up type with a wet process procedure to prepare organic nanocrystals, and organic nanocrystals are obtained as their water dispersion. Numerous numbers of organic compounds are allowed to be a candidate for a targeting of organic nanocrystals by means of using the reprecipitation method. Functional organic nanocrystals have been attracted in a scientific and technological area of materials. In this chapter, first we mention the research back ground of organic nanocrystals, and then introduce the preparation method of organic nanocrystals, i.e. the reprecipitation method, and their improved ones. Then, several kinds of functional organic nanocrystals relating to optoelectrical materials, nanomedicine, and biophotonics are mentioned. Recent topics of organic nanocrystals achieved by several groups are briefly introduced. In this chapter, the topics are proceeding as follows:

1. Back ground of the research of organic nanocrystals
2. Preparation method of organic nanocrystals
3. Several functional organic nanocrystals
4. Recent topics of organic nanocrystals achieved by several groups

2. Back ground of the research of organic nanocrystals

Fabrication of nanocrystals and their nanostructure has been investigated extensively for metals (Ung et al., 1997) and semiconductors (Murray et al., 1993), and many characteristic properties have already been shown. For example, a novel and unique optical property called the quantum size effect (Nakamura, 1992) was found for such inorganic nanocrystals in a size of a few nanometres (e.g. nonlinear optics, semiconductor lasing, and quantum dot applications).

For organic nanocrystals, however, nanocrystals fabrication has so far rarely been investigated, owing to their thermal instability, except for the thermally stable

phthalocyanine and a kind of low molecular weight aromatic compounds which were nanocrystallized by an evaporation method in an inert gas (Granqvist et al., 1976) or by a crystal growth technique in a porous polymer (Matsui et al., 1995). Recently, we have proposed a simple and convenient method for the fabrication of organic nanocrystals, what we call the reprecipitation method (Kasai et al., 1992). In brief, the hydrophobic solution in which hydrophobic compounds dissolved is injected into water, which results in a reprecipitation owing to its insolubility in water to give nanocrystal dispersion. By this method, many kinds of organic compounds such as polydiacetylene (Katagi et al., 1996), phthalocyanine (Yanagawa et al., 1997), perylene (Kasai et al., 1996) and so on can be nanocrystallized successfully. Interestingly, size-dependent optical properties are observed for these organic nanocrystals even in the 100 nm size range, an order of magnitude larger than the scale where the inorganic nanocrystals usually show size-dependent optical properties. These aqueous organic nanocrystals dispersions may have great potential for use in fundamental and applied optics, e.g. as nonlinear optical (NLO) materials having large $\chi^{(3)}$ without optical loss (Kasai et al., 1995) and having easy process ability to other material forms.

Until now, not only the investigation of fundamental optoelectrical properties of organic nanocrystals, but also their interesting physiochemical properties and their peculiar advantages compared to inorganic nanocrystals have been extended to nanomedicine and biophotonics. First we introduce the fabrication technique of organic nanocrystals; the reprecipitation method.

3. Preparation method of organic nanocrystals

3.1 The reprecipitation method

The reprecipitation method, which is a solvent displacement method, was first reported by our research groups (Fig. 1a) (Kasai et al., 1992). It provides a very simple and versatile way to prepare organic nanocrystals dispersions. The method involves a rapid mixing of a small amount of concentrated stock solution of the target compound dissolved in a good solvent with excess of a poor solvent. The great disparity between the solubilities of the target compound in the good and poor solvents, and the good compatibility of the two solvents are essential for this method. The rapid mixing of the stock solution and the poor solvent changes the micro-environment of the target compound molecules. The molecules are exposed to the poor solvent surroundings in a very short time, inducing the nucleation and growth of the molecules to nanocrystals. The size and morphology of nanocrystals can be controlled (Fig. 1b and 1c) by tuning a concentration, temperature, stirring speed, and adding surfactant. Then the precipitation creates nanocrystals dispersed in water. Many kinds of organic compound such as π -conjugate compounds, NLO dyes (Kaneko et al, 2005), fluorescent dyes (Fig. 1d), fullerene (Tan et al., 2008), and several polymers (Ishizaka et al., 2006; Zhao et al., 2009) are candidate for nanocrystals (nanoparticles for polymer). However some kinds of rigid compounds such as phthalocyanine having π - π stack structure are quite hard to be solved in usual organic solvent, thus for the nanocrystal preparation of these attractive functional compound, an advanced preparation technique is required. A supercritical fluid is a candidate for dissolving this problem.

3.2 Supercritical fluid crystallization method

The properties of phthalocyanine are very interesting in both optics and electronics in the fields of nonlinear optics, organic photoconductors, and pigments. Phthalocyanine is known

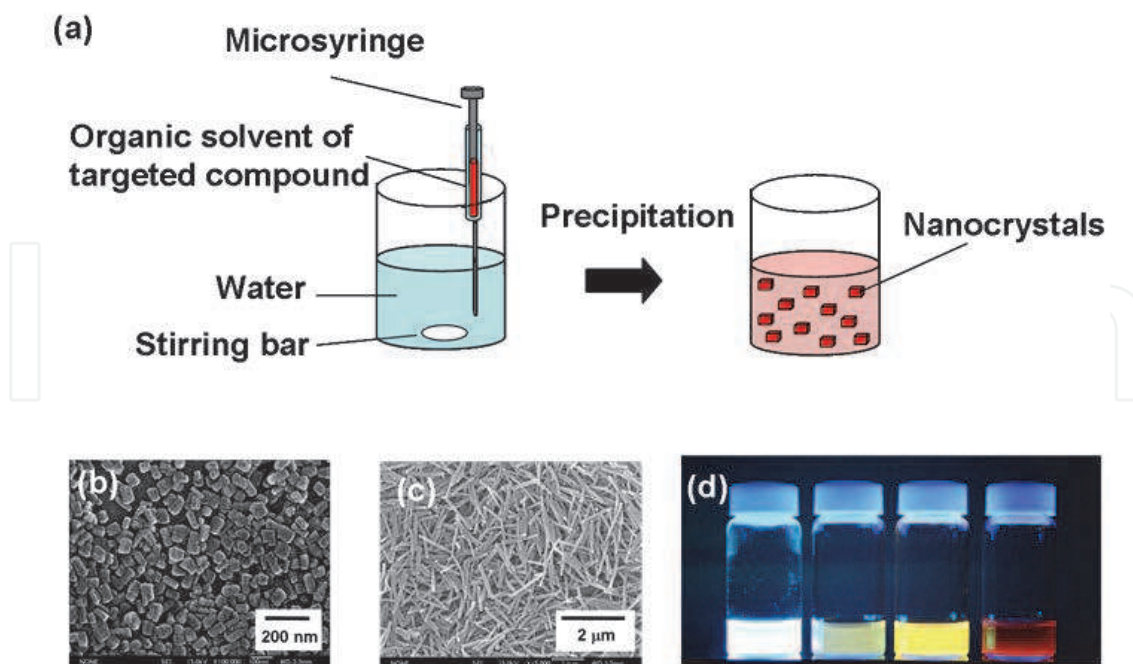


Fig. 1. (a) Scheme of the reprecipitation method. (b,c) Size controlled organic nanocrystals in same compound. (d) Fluorescence images of organic nanocrystals in water.

to have large $\chi^{(3)}$ and ultrafast optical response in the crystalline state (Matsuda et al., 1990).. However, it is almost impossible to make large single crystals of phthalocyanine, because its solubility is very poor in almost all kinds of solvent. Thus, one of the best ways for the application of phthalocyanine crystals would undoubtedly be to make devices with constructed by nanocrystals. Even this, commercial phthalocyanine nanocrystals have been prepared and refined only by the acid-pasting method, and these phthalocyanine nanocrystals have been used as materials for organic photoconductor. However, this method may give rise to environmental problems in the near future due to the use of much sulphuric acid.

On the other hand, supercritical fluid (SCF) has been expected to have a high solubility against insoluble organic compounds, since it shows high solubility under high temperatures and high pressure. Thus, we expected the SCF approach to be an alternative method for making phthalocyanine nanocrystals, instead of the acid pasting method. On the basis of this idea, the use of SCF was examined for the purpose of improving the reprecipitation method. The new method is called supercritical fluid crystallization (SCFC) method (Fig. 2) (Komai et al., 1998). The preparation of phthalocyanine nanocrystals using the SCFC method was used in order to demonstrate this usefulness. The size and modification control of titanly phthalocyanine crystal have been attempted using the reprecipitation method from SCFC. The fabrication *r*-form of titanly phthalocyanine nanocrystals was achieved, which is a hopefully candidate for materials for organic photoconductor. Recently, further application using SCFC method has been developed as new one including several organic pigments and inorganic semiconductors. As shown in this section, the applying the additional outsources energy like SCF to the reprecipitation method is quite useful for extending the preparation possibility of organic nanocrystals. As a further extension, the approach using a microwave irradiation was also demonstrated as a useful procedure for preparing organic nanocrystals.

3.3 Microwave-irradiation reprecipitation method

Recently, as a novel fabrication technique of functional materials, a microwave irradiation process is much noted in the field of organic and inorganic synthesis and nanoparticles. For example, high critical temperature superconductors, mono-dispersed nickel, gold, silver nanoparticles, and organic-metal complexes were successfully prepared by using this technique.

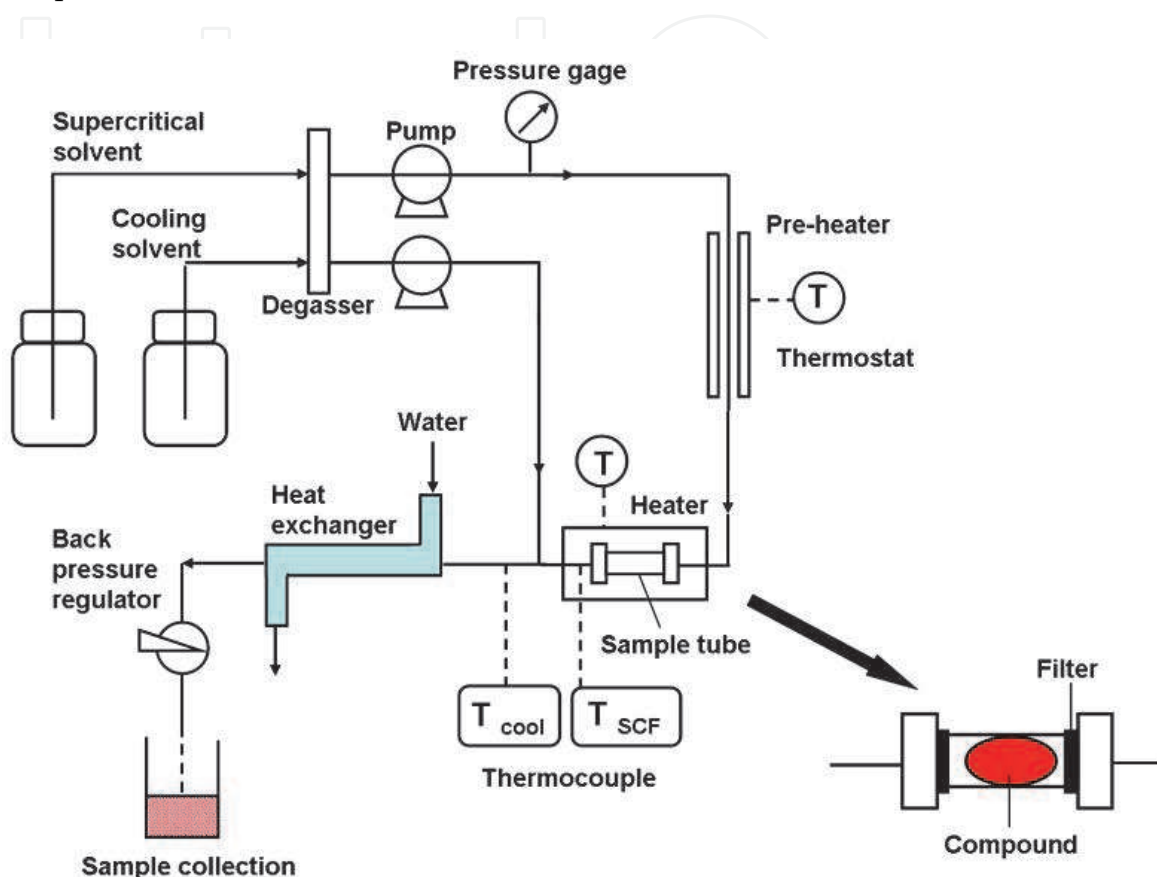


Fig. 2. Scheme of the supercritical fluid crystallization method.

We focused on the unique aspect of microwave at 2.45 GHz. One of the aspects of microwave (2.45 GHz) is that the microwave is well absorbed by water molecule, resulting in effective homogeneous and rapid heating of water is realized. Since nanocrystals are prepared in water environment by the reprecipitation method, we have attempted to apply the microwave-irradiation process to the reprecipitation method for the purpose of fabricating well-defined organic nanocrystals (Fig. 3). Upon microwave-heating was applied to the reprecipitation method, homogeneous and rapid heating increased the homogeneous crystal growth and then the crystallization was completed without particle aggregation. This homogeneous heating resulted in making fine narrow-sized homogeneous nanocrystals dispersed in water (Baba et al., 2000). If the conventional conductive heating such as hot plate heating was used, this gradient heating induced large-sized and random-size distributed crystal growth in aqueous dispersion system.

We demonstrated that the narrow size distributed nanocrystals of TPB, perylene (Fig. 4) (Baba et al., 2000), and DCHD were successfully fabricated within a short time by applying microwave heating just after our conventional reprecipitation procedure. Furthermore, there

was finding that the size and morphology of DCHD nanocrystals and nanofiber were controlled well under using the open- and closed-type vessel (Fig. 5) (Baba et al., 2007a). The next stage of our interest was how to mass produce these attractive organic nanocrystals for the sake of industrial approach.

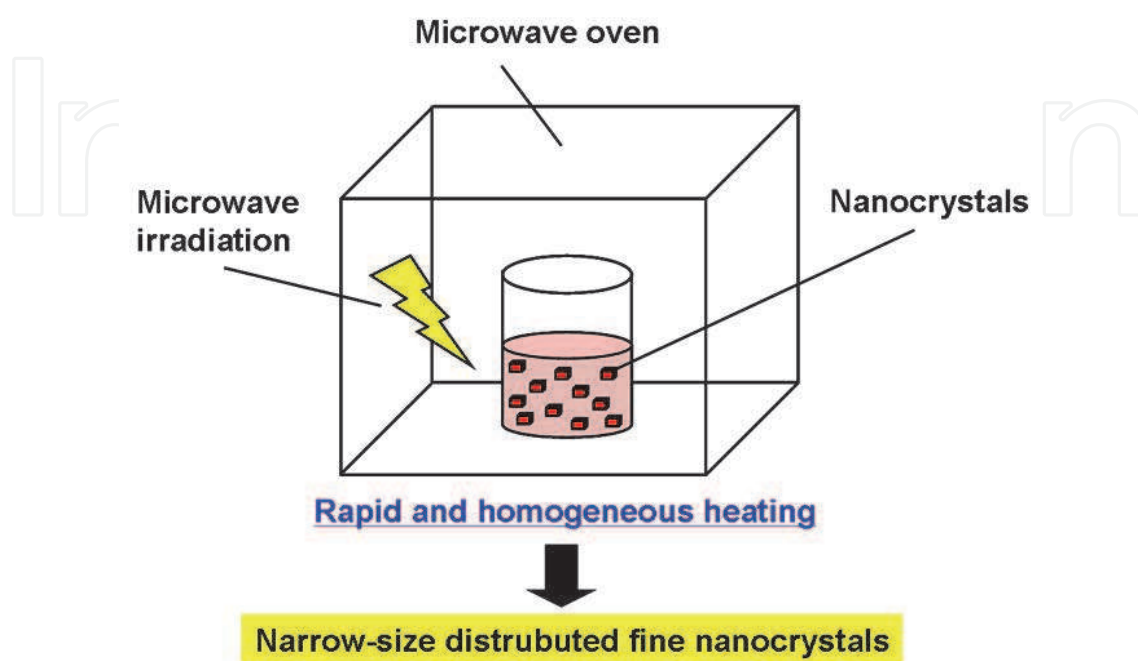


Fig. 3. Scheme of the microwave-irradiation reprecipitation method.

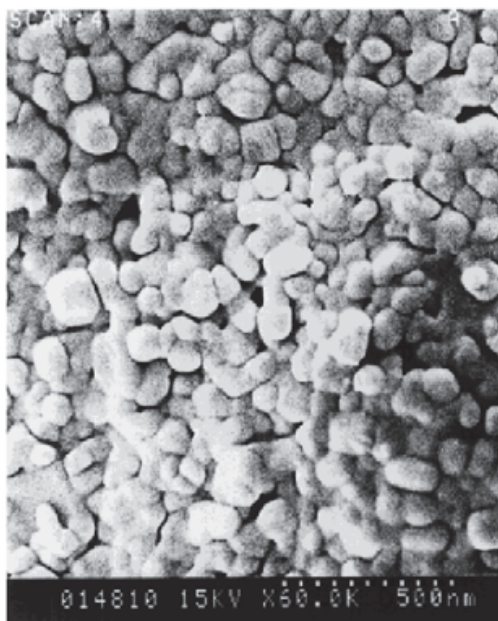


Fig. 4. Perylene nanocrystals prepared by the microwave-irradiation reprecipitation method. (Reprinted from (Baba, et al., 2000): Japanese Journal of Applied Physics. Vol. 39 (2000) pp. L1256-L1258, Part 2, No. 12A, DOI: 10.1143/JJAP.39.L1256. Copyright 2000 The Japan Society of Applied Physics)

3.4 Mass production of organic nanocrystals

The reprecipitation method is an easy and convenient technique to fabricate organic nanocrystals in general. However, only limited amount of nanocrystals dispersion (about several-tens ml) was prepared at once, i.e. the laboratory scale. To overcome this problem, we introduced a pump as an injection apparatus of the reprecipitation method for mass-production of pigment nanocrystals with controlled size and morphology (Ujiye-Ishii et al., 2006).

For mass-production, most efficient conditions of the reprecipitation method have injecting highly concentrated solution with high injection rate. The former condition was achieved by using 1-methyl-2-pyrrolidone (NMP) and the latter was realized by using a high flow-rate pump. Using the injection pump-assisted reprecipitation method, the amount of obtained quinacridone nanocrystals in dispersion was 700 mg per minute at maximum, and then 3.5 g of the nanocrystals were obtained in one experiment. This value was about 17,500 times

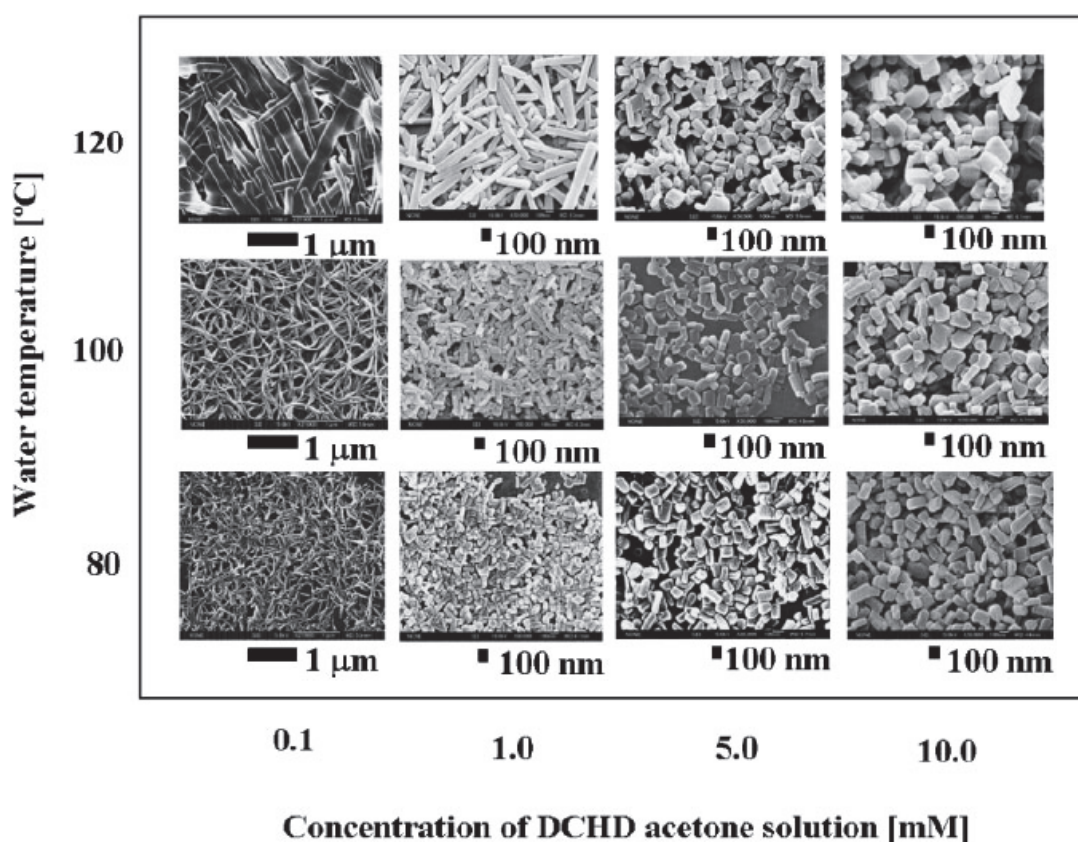


Fig. 5. Poly(DCHD) nanocrystals prepared by the closed-type microwave-irradiation reprecipitation method. (Reprinted from (Baba, et al., 2007a): Japanese Journal of Applied Physics. Vol. 46 (2007) pp. 7558-7561, No. 11, DOI: 10.1143/JJAP.46.7558. Copyright 2007 The Japan Society of Applied Physics)

larger than that obtained by the conventional reprecipitation method with manual injection. The size of quinacridone nanocrystals fabricated was 25–80 nm, which was confirmed by observation using a scanning electron microscope. From the powder X-ray diffraction data, only α -type nanocrystals were obtained. This mass production procedure of pigment nanocrystals is useful for an application of a color filter.

4. Several functional organic nanocrystals

4.1 Color filter using organic pigment nanocrystals

Organic pigments have been widely used in printing and coating industries as the coloring agents of synthetic fibers and plastics. Recent years, some organic pigments have an attention as organic photoconductors such as organic EL materials and electrophotographic photoreceptors. In addition, organic pigments are used for ink-jet inks to produce photographic-quality pictures and for color filters that are essential materials for the full-colorization of digital cameras and liquid crystal displays (LCDs). To increase the performance of the color filter, it is absolutely essential to cancel out the light scattering by reducing the particle size of organic pigments. Yet dyes can be an attractive alternative to overcome this limitation due to the reduced light scattering because they are dissolved in the media and exist in molecule form, however, in order for the dyes to be applied successfully to LCDs manufacturing process, their low thermal stability needs to be improved. Therefore, as the way to reduce the particle size, the breakdown method using beads and/or inorganic salts are commonly used. However, an energy efficiency, inclusion of contaminants such as bead materials (e.g., inorganic salts and zirconia), and a difficulty to reduce the particle size less than 50 nm are causing industrial problems. Therefore, the solution of these problems has been strongly desired. To overcome these problems, mass production procedure of organic pigment nanocrystals by the newly developed reprecipitation method was investigated, and the possibility of their application to color filter for LCDs was evaluated.

To evaluate the prepared organic pigment nanocrystals as a functional material for color filters, it is necessary to significantly increase their preparation amount. For this realization, a highly concentrated pigment solution and an improvement in the injection rate of the solution were necessary. Based on the literature (Ujiye-Ishii et al., 2006), the system using a pulsation-free pump was built. In this newly developed reprecipitation method, it increased the preparation amount of nanocrystals by 104–106 times (Miyashita et al., 2008).

The organic pigment nanocrystals prepared by the reprecipitation method were finer in mono-dispersed property, compared to the conventional products. The average size of pigment nanocrystals prepared by the reprecipitation method was 25 nm and that of the pigments prepared by the breakdown improved milling method was 39 nm, and the former was in finer size dispersion (i.e., mono-dispersion). The relationship between the particle formation mechanism and particle size in the reprecipitation method is also under study. To clarify the reduction of the light scattering that is affected by the reduced size of pigment particles, the light scattering intensity was measured using a goniometer. In LCDs, if the light scattering occurs by pigment particles, the reduction of the display contrast and/or the luminance ratios occurs. Thus this becomes a serious problem when the display is in ON/OFF in LCDs.

It is apparent that the use of pigment nanocrystals prepared by the reprecipitation method can significantly increase the contrast ratio of LCDs, which is one of the most important performances. As a result, a new production process of organic pigment nanocrystals reduced the light scattering by fine size and well dispersed organic pigment nanocrystals prepared by the reprecipitation method.

It was found that organic pigment nanocrystals with the particle size about 25 nm were successfully achieved by the reprecipitation method. Because the fine size-controlled organic pigment nanocrystals lead to very little light scattering, they are considered to be useful for improving the performance of color filters that are an essential component of LCD.

4.2 Organic nanocrystals for organic field effect transistor

The functionality of organic pigment is attracted in electro devices such as organic electro luminescence devices and organic field effect transistor (OFET). Especially, the research of OFET is hot topic toward a future of optical device. Several kinds of electron-hole transfer organic compounds are well investigated. For OFET, carrier mobility is important factor for high quality devices. A π -conjugate polymer, polydiacetylene (PDA), is one of the promising compounds having high carrier mobility. PDA is a unique material, which combine the properties of an essentially one-dimensional, fully conjugated polymer with the ability of single crystalline monomers to polymerize without disruption of the crystallinity (Takahashi, et al., 2002). PDA has the optical properties of large non-linear optical susceptibility and ultra-fast response time as well as a PDA been predicted to present very high charge carrier mobility, up to 10^3 – 10^5 cm²/V s. However the real mobility of PDA crystals measured using time-of-flight technique was found to be 1–10 cm²/V s, and that is comparable to those measured on polyacene molecular crystals such as anthracene or naphthalene. The use of PDA films as an active layer of OFET is very promising task, however the pure electrical conductivity of these films have restricted their application. Thus to improve the conductivity is attracted work. Several attempts to improve the electrical conductivity have been reported; chemical doping into the stage of monomer crystals and in the course of solid-state polymerization, chemical doping into soluble polydiacetylenes, chemical doping into a Langmuir–Blodgett film of PDA, ion implantation to PDA bulk crystals, and using a scanning tunneling microscopy probe tip to fabricate linear PDA nanowires. Recently, the maximum conductivity for chemically doped PDA crystals has been reported to be as high as 10^2 S/cm. As a widely held opinion, one of the big issues in increasing the conductivity of PDA is that its rigid crystalline lattice prevents the dopant from penetrating into PDA bulk crystals. This was especially the case in 1,6-di-*N*-carbazolyl-2,4-hexadiyne (DCHD).

To overcome the difficulty of chemical doping to PDA, we tried chemically doping into the nanocrystals of PDA, because PDA nanocrystals are known to have a softened crystal lattice (Baba, et al., 2006) and a large surface area, compared with bulk crystals, and demonstrated almost the highest conductivity of chemically doped PDA ever reported (Baba, et al., 2008). Figure 6 shows that the single layered poly-DCHD nanocrystals on slide glass and their specimen for measuring their conductivity. The success in chemical doping was achieved because poly-DCHD nanocrystals have a large surface area and softened crystal lattices, which allows chemical dopant species to diffuse easily into poly-DCHD nanocrystals in good contrast to the case of bulk crystals. Actually, nanostructure showed unique conformation change during solid state polymerization. Nanostructure have showed crack-less action during polymerization. This also showed that the nanocrystal has softened crystal lattice and has flexible stricture (this is mentioned in the next section). Thus, the PDA nanocrystals can accept the dopant. Aiming at the fully doped single crystalline nanocrystals of PDA, the effects of crystal size, morphology, and several kinds of chemical dopant species, which would increase the conductivity of PDA, are now under investigation.

As future approach, achieving the one dimensional array of the PDA nanofibers layered on the surface of devices is promising approach for high conductivity. We previously reported the one dimensional array of nanofibers. Furthermore, interesting finding concerning morphology changes during solid-state polymerization of PDA nanofibers were reported by our group, which related to topochemical study. This was because the softened crystal lattice of nanocrystals.

4.3 Solid state polymerization of polydiacetylene: topochemical polymerization

The research of the topochemical polymerization has been reported extensively since the 1960s, and PDA is the most attracted one. PDA also has been attracted because this π -conjugated polymer system has received much attention as conductive and non-linear optical materials. However, the accumulation of strain in bulk crystal during the solid-state

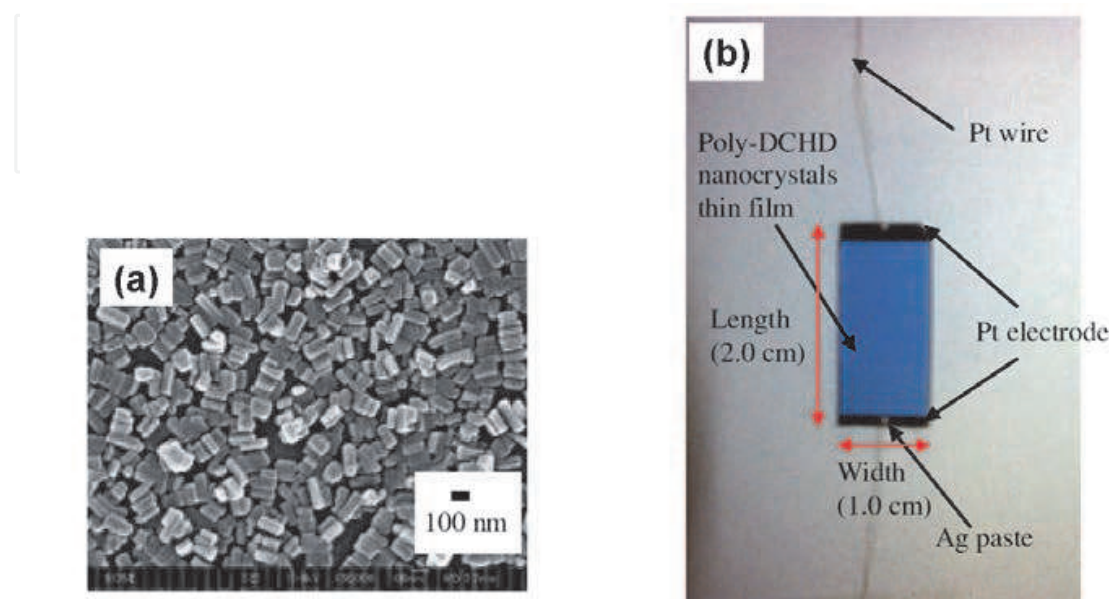


Fig. 6. (a) Single layered poly(DCHD) nanocrystals on quartz slide glass. (b) Image of the specimen for conductivity measurement of single layered poly(DCHD) nanocrystals. (Reprinted from (Baba, et al., 2008): Japanese Journal of Applied Physics., Vol. 47 (2008), pp. 3769-3771, No. 5, DOI: 10.1143/JJAP.47.3769. Copyright 2008 The Japan Society of Applied Physics)

polymerization results in crushing crystal structure, and the rate of polymeric conversion does not occur with high efficiency. We found that the polymerization of nanocrystals achieved high quality polymeric crystal because the strain accumulated in nanocrystals was easily released (Baba, et al, 2006). Nanofibers prepared by the reprecipitation method had an average length of 10 μm and width of 50 nm. We found interesting behavior of morphological change of nanofibers during the stage of the solid-state polymerization. DCHD monomer nanofibers, which were fabricated by the reprecipitation method, were worm-like before solid-state polymerization. Interestingly, worm-like nanofibers converted into straight-like ones through the solid-state polymerization. This phenomenon indicated that the lattice in nanofibers was generally soft, compared with that of bulk crystals. The crystalline nanofibers are useful for the estimation of a nonlinear optical property and a conductivity of a single polymer chain.

4.4 Linear and nonlinear optical property of organic nanocrystals

PDA crystals have attractive nonlinear optical properties. Our interest is the nonlinearity occurred in nanocrystals. The fabrication of polydiacetylene nanocrystals with varied size was achieved using the reprecipitation method. The size effect on the absorption spectra, which was a characteristic to organic nanocrystals, has been experimentally verified. An

important point is that size-dependent blue-shift appears at a size an order of magnitude larger than that of semiconductors and metals. That is due to the lattice vibration must become highly frequent with increasing temperature and also with decreasing crystal size. Actually, these thermal effects and sizes were clearly related to phonons in the nanocrystals lattice. The obtained $\chi^{(3)}$ was the order of 10^{-9} esu (Nakanishi & Katagi, 1998). Thus, we believe PDA nanocrystals is promising NLO materials. These attractive data was obtained in two-dimensional structured thin films of polymer matrix. Further our interest was constructing the three-dimensional (3-D) structure of nonlinear materials such as photonic crystals.

Photonic crystals have been a subject of considerable interest for more than a decade. A great deal of effort has been put into preparing highly ordered photonic crystals for the visible spectral range. Initial studies were directed toward the linear optical properties of these crystals, but more recent studies have focused on nonlinear processes in photonic crystals, and dramatic enhancements of these properties have been reported (Markowicz, et al., 2004).

Our interest is to study the optical properties of highly ordered 3-D arrays of polydiacetylene nanocrystals, since 3-D arrays formed by mono-dispersed particles in the range of 10 nm to 1 μ m, referred to as colloidal crystals, show some special optical properties and potential applications, particularly in photonic devices. However, polydiacetylene nanoparticles are usually polyhedral and multi-dispersed. Their morphology prevents them from forming large-scale densely packed 3-D structures because the particles that form colloidal crystals are required to have a size variation of less than 5%. Polystyrene is one of the important materials in the fabrication of colloidal crystals, since uniform spherical polystyrene particles were easily synthesized by soap-free emulsion polymerization. When polydiacetylene nanocrystals are enclosed within uniform spherical polystyrene particles, the resulting composite particles are used to construct 3-D arrays of nonlinear materials. We reported the fabrication and characterization of spherical mono-dispersed composite particles consisting of 1,6-di(N-carbazolyl)-2,4-hexadiyne (DCHD) nanocrystals cores and polystyrene shells. We succeeded in preparing mono-dispersed composite particles consisting of poly-DCHD cores and polystyrene shells (Wei, et al., 2003). Their 3-D structure is attractive for investigating their nonlinear optical properties.

Recently, an interest of photonic crystals has also been directed toward studying the effect of disorder in photonic crystals. Prasad's group reported on a type of disorder in photonic crystals in which only a random variation of refractive index is introduced, without creating any structural or positional disorder, which was referred to be such disordered photonic crystals as photonic crystal alloys (Tiryaki, et al., 2004). The vertical deposition colloidal crystal method to produce three-dimensional photonic crystal alloys of polystyrene and poly(methyl methacrylate), 300 nm spheres in varying compositions were used. This photonic crystal alloys provided a convenient medium to compositionally tune the bandgap and the wavelength of a phase-matched nonlinear optical response. Prasad's group is saying that the use of photonic active components (such as dye-doped spheres) allows one to conveniently create microcavities and study cavity electrodynamics.

4.5 Nanomedicine: Drug delivery system using drug nanocrystals

Numerous commonly used pharmaceutical drugs are hydrophobic in nature. Thus, special formulations are required to make their aqueous dispersion for these drugs delivery.

Usually, surfactants or other nanoparticle-based delivery vehicles are used. Once systemic administration of these drugs, if the drug target cancer organ, such drug-doped carriers are preferentially taken up by tumour tissues based on the “enhanced permeability and retention effect”. The carriers include liposomes, polymeric micelles, oil dispersions (micelles), ceramic, hydrophilic drug-polymer complexes and polymeric nanoparticles. However many surfactants themselves tend to increase the systemic toxicity of the drug formulation. Therefore, there is increasing interest in the development of novel drug formulation and delivery methods without any external agents such as surfactants or other carrier vehicles. One method proposed for dispersion of hydrophobic compound in water, the reprecipitation method was used as demonstration.

Prasad's group have prepared the nanocrystal formulation of a hydrophobic drug for photodynamic therapy (PDT) and compared its efficacy with the conventional surfactant-based formulation (Baba, et al., 2007b). PDT is a promising new modality for the treatment of a variety of cancers and some dermatological and ophthalmic diseases. The main advantage of PDT is the capability to localize the treatment, by using selective light exposure to the tumor site. Typical PDT treatment involves systemic administration of a photosensitizer drug, then localized light exposure at the tumor site using near-infrared light. After being excited with light, these photosensitizer molecules can transfer their excited-state energy to molecular oxygen in the surroundings, forming reactive oxygen species such as singlet oxygen. The locally generated reactive oxygen species destruct various cellular compartments, resulting in irreversible damage to tumor cells. The major disadvantage for successful clinical PDT is the poor water solubility of photosensitizing drugs. Thus, making their stable formulation for systemic administration is highly challenging. To overcome this difficulty, a stable dispersion of these drugs into aqueous systems is achieved using delivery vehicles. However, allergic reactions and their sustained *in vivo* toxicities are caused by the carrier vehicles. Therefore, the ideal formulation for safe and efficient PDT should involve the minimal number of additional agent such as carrier. To overcome these problems, nanocrystals, which were monodispersed with diameter 100 nm (ζ -potential: -40 mV), were prepared by the reprecipitation method (Baba, et al., 2007b).

There was interesting finding that though the fluorescence and photodynamic activity of the drug nanocrystals were initially quenched in aqueous media. However, both recovered under *in vitro* and *in vivo* conditions (Baba, et al., 2007b). This recovery of drug activity and fluorescence was attributed to the interaction of nanocrystals with blood serum or other intracellular components (e.g., serum albumin), resulting in conversion of the drug nanocrystals into the molecular form. Efficacy of the nanocrystals formulation *in vitro* and *in vivo* was found to be comparable with that of the same drug formulated in the conventional delivery vehicle.

These results have not only mentioned the potential of using pure drug nanocrystals for PDT, but also this approach eliminates the need of any external agents such as surfactants or other carrier vehicles for drug delivery. Further studies are expected to increase the efficacy of nanocrystals by controlling their size that may affect long-term *in vivo* circulation and accumulation in the tumor tissue. Potentially, this method of drug formulation can be applied not only for PDT drugs, but also for delivery of other therapeutic drugs including imaging agents such as fluorescent dyes for biophotonics (e.g., bioimaging).

4.6 Bioimaging using fluorescent dye nanocrystals

Fluorescence microscopy is one of the most versatile imaging techniques in biomedical research. That allows the non-invasive imaging of cells and tissues with molecular specificity. Such imaging requires a fluorescent dye to enter cells and tissues prior to visualization. Currently used dyes include members of the coumarin, rhodamine, fluorescein, and carbocyanine families. One of them, 3,3'-Diocetadecyloxacarbocyanine perchlorate [DiO; DiOC18(3)] is the long-chain dialkylcarbocyanine dye, and most commonly used for the visualization of anterograde and retrograde neuronal tracers in living cells. This lipophilic carbocyanine is also employed in many other applications, including cytotoxicity assays, the labeling of lipoproteins, and the tracking of cell migration and lipid diffusion in membranes through fluorescence recovery after photobleaching. The hydrophobic nature of these dyes means that, in many cases, organic solvents [e.g., dimethylformamide, dimethylsulfoxide (DMSO)] and surfactants are required for successful cell imaging. However, unfortunately, organic solvents and surfactants themselves tend to increase cytotoxicity *in vitro* and *in vivo*. On the other hand, the direct applications of micron-sized crystals have also been investigated, although such crystals are probably not small enough to allow the diffusion of dyes into cells, i. e. not efficient imaging approach.

In addition to DiO dyes, many other fluorescent dyes are hydrophobic in nature – including perylene, a widely studied hydrophobic material that functions with a high quantum yield in organic electroluminescence devices. Although it is potentially useful for bioimaging, the preparation of aqueous dispersions of perylene dyes requires special formulation techniques, similar to those for DiO. The reprecipitation method was used to solvent-free and non-invasive bioimaging. We reported an organic solvent-free bioimaging method employing fluorescent dye nanocrystals prepared using the reprecipitation method and their application to *in vitro* fluorescence confocal imaging (Baba et al., 2009, 2010).

These nanocrystal formulations allowed efficient fluorescence confocal imaging of living cells *in vitro*, with performances almost identical to those obtained by treatment using a conventional organic solvent. This nanocrystal formulation approach to *in vitro* bioimaging in cultures eliminates the need for external solubilizing agents (e.g., organic solvent or surfactant), which usually tend to increase cytotoxicity. We expect that this method can be used with a wide range of hydrophobic organic fluorophores. As an advanced functional bioimaging tool, our team recently have developed thermoresponsive fluorescent nanocrystals, which will be useful for temperature-dependent cell imaging as well as photodynamic cancer therapy.

4.7 Thermoresponsive behaviour of fluorescent organic nanocrystals

After the first introduction of a temperature-responsive polymer, poly(N-isopropylacrylamide) (PNIPAM) (Heskinsa & Guillet, 1968), numerous studies on this polymer have been reported. The fundamental findings have been applied in various fields such as drug delivery, regenerative medicine, (Nishida, et al., 2004) and analytical chemistry. The property of this polymer is that when the temperature of the aqueous solution where the polymer is dissolved increases above the lower critical solution temperature of the cloud point, the polymer shows phase separation. The hydrophobic groups in the polymer form insoluble aggregates, turning the solution cloudy (Chen & Hoffman, 1995). Using this characteristic of PNIPAM, fluorescent dyes covalently linked to PNIPAM showed on-off fluorescent switching properties above and below the critical

temperature. On the other hand, we demonstrated the thermoresponsive behaviour of fluorescent organic nanocrystals using PNIPAM in an aqueous system for the first time (Baba, et al., 2011). For the preparation of thermoresponsive fluorescent organic nanocrystals, fluorescent dyes of perylene, quinacridone, and zinc phthalocyanine were used. As a result, an on-off switching of fluorescence intensity was observed below and above around cloud point ($\sim 35^{\circ}\text{C}$). This thermoresponsive behaviour of fluorescent organic nanocrystals in the aqueous system was stably repeatable. As an extension of this research, this research finding indicates that the fluorescence properties of organic nanocrystals can be controlled using the phase-transitional functional polymer system, where the key factors for stimulation are not only limited to temperature but also light and pH. This fundamental finding of tuneable fluorescence optical property of organic nanocrystals will have several applications such as thermosensitive fluorescence bioimaging of living cells/tissues using PNIPAM-based fluorescent dye nanocrystals; the on-off switching logic gate for optical devices; and medical treatment by photodynamic therapy using PNIPAM-based on-off switching photosensitizing nanocrystals, where the drug efficacy can be controlled by temperature on demand. We believe this finding will be applied in multidisciplinary fields such as nanomedicine, nanobiology, tissue engineering, regenerative medicine, and applied optical physics.

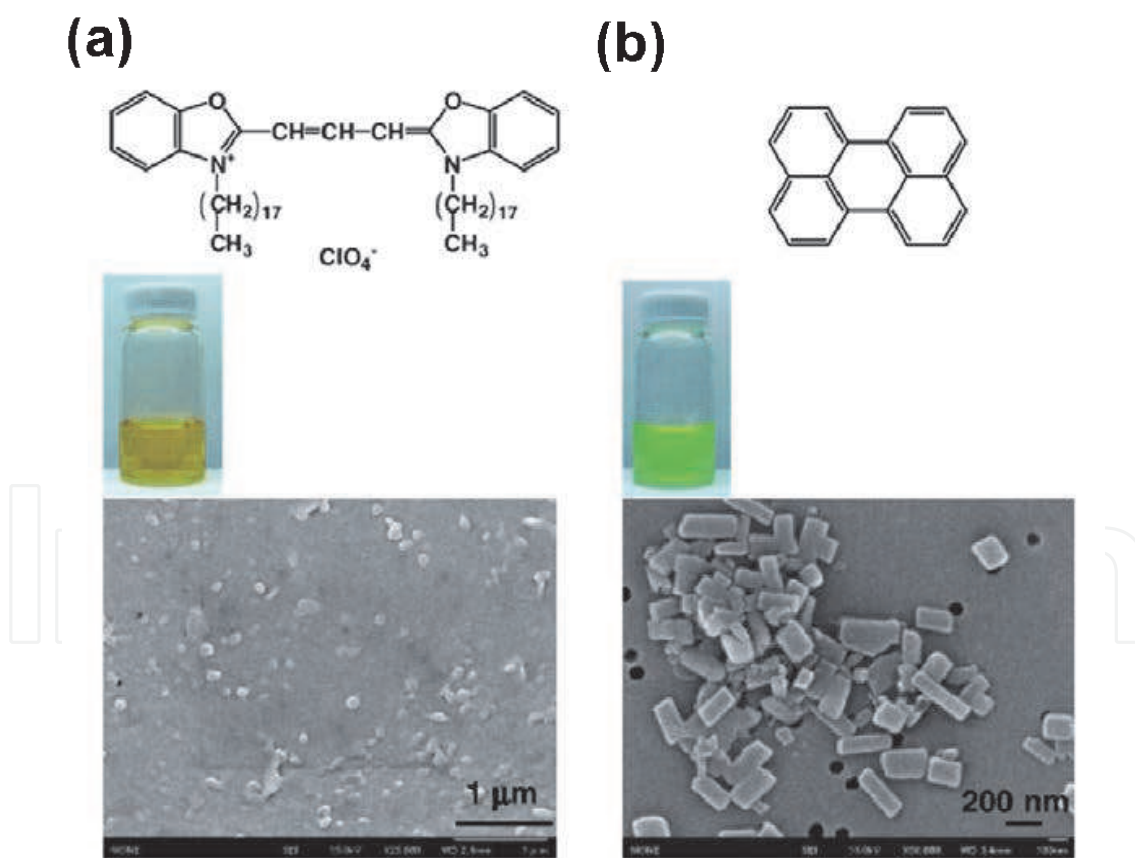


Fig. 7. Chemical structure, photographs of dispersion, SEM images of (a) DiO and (b) perylene. (Reprinted from (Baba, et al., 2009): Japanese Journal of Applied Physics. Vol. 48 (2009), 117002 (4 pages), DOI: 10.1143/JJAP.48.117002. Copyright 2009 The Japan Society of Applied Physics)

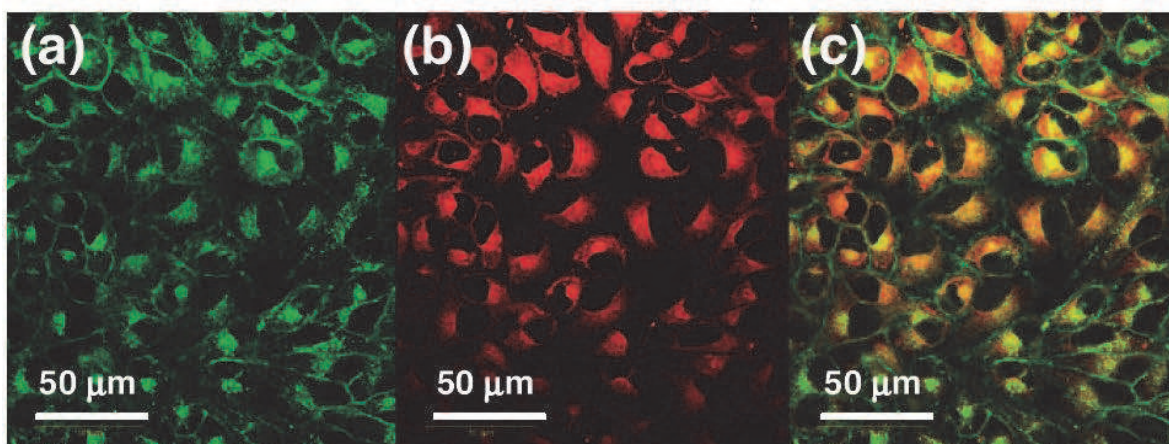


Fig. 8. Confocal fluorescence images of culture cells *in vitro*. Dyes used for the staining are (a) DiO and (b) perylene. (c) Double staining image that is overlapped pictures of (a) and (b). (Reprinted from (Baba, et al., 2009): Japanese Journal of Applied Physics. Vol. 48 (2009), 117002 (4 pages), DOI: 10.1143/JJAP.48.117002. Copyright 2009 The Japan Society of Applied Physics)

5. Recent topics of organic nanocrystals achieved by several groups

Now a day, with using the reprecipitation method, a series of functional organic nanocrystals/nanoparticles were successfully fabricated by several research groups. For example, nanocrystals from perylene and a perylene derivative were prepared and the spectroscopies of single nanoparticles were studied. Nanoparticles were prepared from β -carotene and observed the influence of both supramolecular structure and particle size on the absorption spectra. The size dependence of the luminescence and the enhanced emission of the nanoparticles prepared with this method were studied in Yao's group (Fu & Yao, 2001) and Park's group (An, et al., 2002). One of the interesting feature occurred in

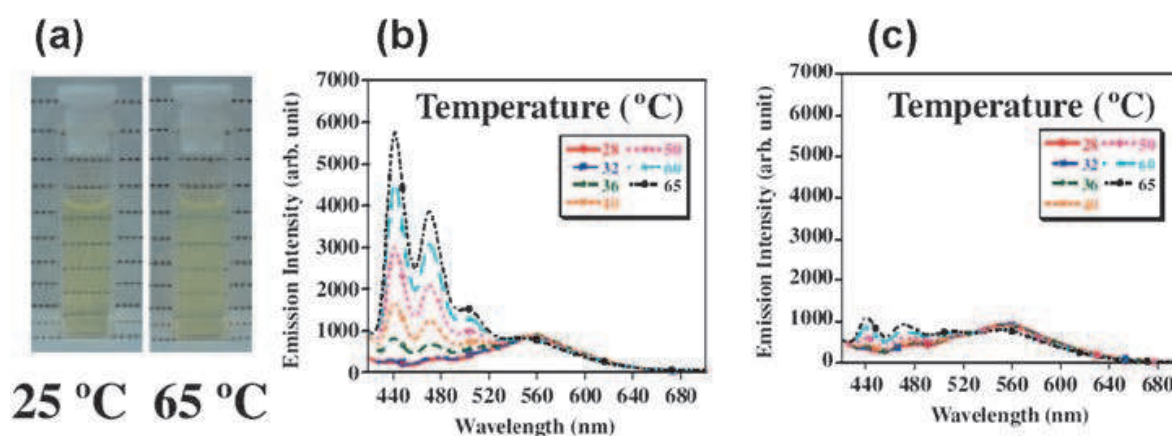


Fig. 9. (a) Photographs of perylene nanocrystals dispersion with PNIPAM at 25 (left) and 65 °C (right). Fluorescence spectra of the nanocrystals (b) with and (c) without PNIPAM. (Reprinted from (Baba, et al., 2011): Japanese Journal of Applied Physics. Vol. 50 (2011), 010202 (3 pages), DOI: 10.1143/JJAP.50.010202. Copyright 2011 The Japan Society of Applied Physics)

nanocrystals, recently Park' group reported a phenomenon named aggregation induced enhanced emission (AIEE). Here, enhanced emission instead of fluorescence quenching was observed in the solid state for some specific fluorophores. In general, the fluorescence efficiency of organic chromophores decreases in the solid state, as a result of concentration quenching, even though they show high fluorescence efficiency in solution. Park's group reported AIEE from organic nanoparticle. First, Park's group synthesized the organic molecule 1-cyano-trans-1,2-bis-(40-methylbiphenyl)ethylene (CN-MBE), and then prepared the corresponding nanoparticles. It was interesting that although the fluorescent from CN-MBE solution was quite weak, the nanoparticles emitted a quite strong photoluminescence. It was considered that the aggregation induced the planarization of the CN-MBE molecules in the nanoparticles, which in turn resulted in the strong intermolecular interactions causing a specific aggregation that was good for efficient emission. This phenomenon was specific to nanoparticles and not to bulky crystals.

Not only the above mentioned optical properties, but also some other optoelectronic properties of organic nanomaterials have been reported in recently. For example, the electronic conductance through organic nanowires was investigated. The Tetracyanoquinodimethane (TCNQ) charge transfer complexes nanowires and field emission properties of tris(8-hydroxyquinolino)-aluminum (Alq 3) nanowires were reported. The field-effect transistors (FETs) based on single-crystalline organic one-dimensional nanomaterials were fabricated, and also lasers have proved to be another promising application for organic one-dimensional nanomaterials. The optical waveguiding properties of organic nanowires were reported. The details are well reviewed in the literature written by Yao's group (Zhao, et al., 2008).

6. Conclusion

In this chapter, first we explained the preparation method of organic nanocrystals and their improved ones. The reprecipitation method is very useful technique for fabricating several kinds of functional organic nanocrystals. Supercritical fluid crystallization method, microwave-irradiation method, and mass production method extend the potential of the reprecipitation method. Then, several kinds of functional organic nanocrystals including recent topics achieved by several research groups were introduced. The research trend of functional organic nanocrystals had begun with a series of optoelectronic materials, and recently several functional organic nanocrystals were revealed to be useful for nanomedicine such as drug delivery system using pure nanocrystal form of drugs as well as organic solvent free confocal fluorescence imaging of living cells *in vitro*. The unique finding of thermoresponsive behaviour of fluorescent organic nanocrystals will be quite useful for bioimaging, regenetec medicine, applied optics, etc. Toward the future works of functional organic nanocrystals, their basic research and application will much more extend to the fields such as optelectronic materials, applied optics as well as nanomedicine, regenetec medicine, and biophotonics.

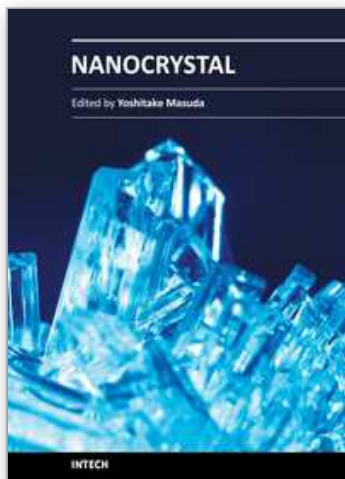
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Phone: +86-21-62489820
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