Contents lists available at ScienceDirect

Dyes and Pigments

journal homepage: http://www.elsevier.com/locate/dyepig

Novel Norrish type I flavonoid photoinitiator for safe LED light with high activity and low toxicity by inhibiting the ESIPT process

Jian You^{a,b}, Ding Cao^a, Tianyu Hu^a, Yaoyao Ye^a, Xiaoqin Jia^a, Hui Li^a, Xiaotong Hu^a, Yingying Dong^a, Yufan Ma^a, Tao Wang^{a,b,*}

^a Department of Organic Chemistry, College of Chemistry, Beijing University of Chemical Technology, Beijing, 100029, PR China
^b State Key Laboratory of Optoelectronic Materials and Technologies, Sun Yat-sen University, Guangzhou, PR China

ARTICLE INFO

Keywords: Photopolymerization Photoinitiator Flavonoid Low-toxicity High activity

ABSTRACT

In this study, flavonoid with N,N-diphenylamino group, 2-(4-(diphenylamino)phenyl)-3-hydroxy-4H-chromen-4one (3HF-OH) was designed and synthesized as low-toxicity photoinitiator for photopolymerization under safe visible LED sources, however, low photoinitiation activity of 3HF-OH was found due to the excited state proton transfer (ESIPT) process. Hence, by replacing the 3-position hydroxyl group of 3HF-OH with benzoyl chloride and benzenesulfonyl chloride, flavonol carboxylate (3HF-C) and flavonol sulfonate (3HF-S) were synthesized, respectively. 3HF-C and 3HF-S showed not only one-component photoinitiating activity but also two-component photoinitiating activity when they were used with triethanolamine (TEOA) and iodonium salt (ONI) under safe, long-wavelength LED soft light sources. Photopolymerization kinetics reveals that photoinitiator 3HFs at low concentration exhibits the high polymerization rate and conversion. Results also showed that 3HF-S has much higher photoinitiation activity during photopolymerization compared with 3HF-OH and 3HF-C. The high extinction coefficient and aggregation-induced emission (AIE) characteristics of 3HF-S were observed, which proved that reducing the photoinitiator usage can effectively progress the photopolymerization activity. At the same time, the low usage of 3HF-S further reduces the toxicity of the cured material. Through electron spin resonance (ESR) experiment, the photoinitiation and sensitization mechanisms of these photoinitiators were observed. The school badge structure of hydrogels could be successfully 3D printed with 3HF-S and the stiffness of the structure was sufficient for further processing without breaking the structure. Moreover, the use of the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) method confirmed the lower toxicity for the final photopolymer provided.

1. Introduction

In photopolymerization technology, the photoinitiator is the most critical and important species in the entire system [1]. However, the photoinitiator cannot be completely consumed in the photopolymerization and easily migrates out of the cured surface, which has the potential to cause corresponding toxicity and environmental pollution [2–6]. Therefore, the development of low-toxicity and high-efficiency photoinitiators is an important aspect in photopolymerization technology. There are two main ideas for the development of low-toxicity photoinitiators: (1) to synthesize macromolecular photoinitiators to reduce migration in photocurable resins and (2) to use the skeleton structure of small molecules of natural products to design and synthesize highly efficient photoinitiators [7,8]. The former

introduces macromolecular chains, which usually reduces the photoinitiating activity of the initiating molecule, while the amount of photoinitiator used increases, affecting the final properties of the cured resin. The latter produces initiators that are usually biocompatible and can avoid the low photoinitiation activity of macromolecular initiators.

Flavonols are ubiquitous in fruits and vegetables. Hence, flavonols generally show extremely low biotoxicity and good biocompatibility to biological organisms [9–13]. Flavonol and its various derivatives are widely used in cell imaging and fluorescent probe studies, and all show low cytotoxicity [14–17]. Flavonol is not only a natural product but also a type of fluorescent molecule with excited state intramolecular proton transfer (ESIPT) [18–20]. The ESIPT refers to the process of proton transfer that occurs between the proton donor and the proton acceptor inside the excited state molecule when the fluorescent molecule is

https://doi.org/10.1016/j.dyepig.2020.108865

Received 27 July 2020; Received in revised form 12 September 2020; Accepted 12 September 2020 Available online 16 September 2020 0143-7208/© 2020 Published by Elsevier Ltd.







^{*} Corresponding author. Department of Organic Chemistry, College of Chemistry, Beijing University of Chemical Technology, Beijing, 100029, PR China. *E-mail address:* wangtwj2000@163.com (T. Wang).



Scheme 1. ESIPT property of 3HF.

excited by light. Both the directly excited state (N *) and the base tautomeric excited state (T *) formed by the ESIPT process can emit fluorescence (Scheme 1). Compared with the electron transfer process, the rate of proton transfer is faster, and the excited state T * of the base tautomer produces long-wavelength strong fluorescence emission. Therefore, flavonol and its derivatives are an important class of fluorescent probe molecules.

Lalevée et al. found that some flavonol derivatives linked to conjugated aromatic hydrocarbons have photosensitivity activity under longwavelength LED light sources [21]. Flavonol (3HF) can be used with amino acids (e.g., *N*-phenylglycine (NPG)) as a low-toxicity visible light initiator for thick samples or free radical polymerization of methacrylate in composites [8]. Furthermore, the effect of different substituents on the photopolymerization of flavonols was discussed, and the initiation rules and mechanisms of the different substituents of flavonols were given [22]. It was found that the flavonol ESIPT process is a competitive process of the photoinitiated process. The strong fluorescence process generated by the hydrogen atom transfer limits the charge transfer sensitization ability and direct initiation ability of the flavonol dye molecules in photopolymerization.

If the hydroxyl group of flavonol compounds is etherified or esterified, it can inhibit the proton transfer process in its excited state molecules, thereby reducing the fluorescence intensity and increasing the triplet lifetime, which results in an increase in its activity during photopolymerization. To obtain a low-toxicity initiator with high-efficiency initiating activity under safe long-wavelength LED soft light sources, we synthesized 2-(4-(diphenylamino)phenyl)-3-hydroxy-4H-chromen-4one (3HF-OH). Through the introduction of triphenvlamine electron donor, we were able to improve the charge transfer ability in the molecule and extend the absorption wavelength. Consequently, the absorption wavelength requirements of long-wavelength LED soft light sources are satisfied. Furthermore, we synthesized flavonol sulfonate (3HF-S) and flavonol carboxylate (3HF-C) by replacing the 3-position hydroxyl group with benzenesulfonyl chloride and benzoyl chloride. 3HF-S and 3HF-C inhibit the ESIPT process, reduce the fluorescence intensity, and improve the photosensitivity with the introduction of ester groups. Moreover, we performed acid production experiment, density functional theory (DFT) calculations, and electron spin resonance (ESR) experiments.

2. Experimental details

2.1. Synthesis of the 3HFs

2.1.1. Synthesis of 2-(4-(diphenylamino)phenyl)-3-hydroxy-4H-chromen-4-one (3HF–OH)

Sodium hydroxide (2.0 g, 0.05 mol) was added to a 100 mL round bottom flask, dissolved in water (5.0 mL), the temperature was lowered to room temperature, and then ethanol (30 mL) was added; Next, 2hydroxyacetophenone (6.0 mmol) and 4-(diphenylamino)benzaldehyde (6.0 mmol) were added, and diluted with ethanol (20.0 mL). After 12 h of reaction, 30% Hydrogen peroxide (H_2O_2) (2.0 mL) was added directly, and the reaction was continued for 12 h. The reaction solution was neutralized with concentrated hydrochloric acid to neutrality. Water was then added to dissolve the inorganic salts produced by the neutralization. At that time, a large amount of solid precipitated. The solid was filtered, and then recrystallized from ethanol. Dark yellow solid. Yield:65%. Mp: > 200 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.15–8.12 (m, 2H), 7.68 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.42–7.38 (m, 1H), 7.33–7.30 (m, 4H), 7.19–7.16 (m, 5H), 7.13–7.10 (m, 3H).¹³C NMR (101 MHz, CDCl₃) δ 172.9, 155.2, 149.6, 146.8, 145.5, 137.6, 133.3, 129.5, 128.8, 125.5, 125.4, 124.4, 124.1, 123.5, 121.2, 120.7, 118.1. IR (KBr, (cm⁻¹)): 3231 (O–H), 1596 (C==O), 1561 (C=C), 1064 (C–O); HRMS (ESI) calculated for C₂₇H₁₉NO₃ 406.1438 [M+H]⁺; found 406.1433 [M+H]⁺.

2.1.2. Synthesis of 2-(4-(diphenylamino)phenyl)-4-oxo-4H-chromen-3-yl benzenesulfonate (3HF-S)

The 3HF-OH (5 mmol) was added to a 100 mL round bottom flask, dissolved in dichloromethane (20.0 mL), and then triethylamine (10.0 mmol) was added. Next, the benzenesulfonvl chloride (10.0 mmol) was dissolved in dichloromethane. The mixed solution was slowly added dropwise to the round bottom flask under ice bath conditions. After the mixed solution is added dropwise, the reaction at room temperature for 4 h. The organic phase was washed 3 times with H₂O. After drying over anhydrous Na₂SO₄, the solution was concentrated and purified by silica gel column chromatography using PE/EA to obtain the pure product (3HF–S) as yellow crystals. Yellow solid. Yield:82%. Mp: 112–114 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (dd, J = 8.0, 1.5 Hz, 1H), 8.01 (dd, J =8.4, 1.2 Hz, 2H), 7.85-7.81 (m, 2H), 7.70-7.63 (m, 2H), 7.53-7.50 (m, 3H), 7.42–7.38 (m, 1H), 7.37–7.33 (m, 4H), 7.16 (dd, *J* = 12.6, 7.4 Hz, 6H), 7.01-6.99 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 172.3, 158.7155.2, 150.8, 146.4137.5, 133.9, 132.6, 130.1, 129.6, 128.7, 128.5, 126.9, 126.2, 126.0, 125.2, 124.7123.9, 121.0, 119.7, 117.9. IR (KBr, (cm⁻¹)): 1591 (C=O), 1503 (C=C), 1059 (C-O), 978 (S=O); HRMS (ESI) calculated for C₃₃H₂₃NO₅S 546.1670 [M+H]⁺, found 546.1683 [M+H]⁺.

2.1.3. Synthesis of 2-(4-(diphenylamino)phenyl)-4-oxo-4H-chromen-3-yl benzoate (3HF-C)

Compound 3HF–C was synthesized from benzoyl chloride by using a similar procedure described above for 3HF–S. Yellow solid. Yield:85%. Mp: > 200 °C. ¹H NMR (400 MHz, DMSO- d_6) δ 8.16 (d, *J* = 7.5 Hz, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 7.4 Hz, 1H), 7.89 (t, *J* = 7.4 Hz, 2H), 7.79 (dd, *J* = 14.5, 7.9 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.53 (dt, *J* = 19.4, 7.5 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 4H), 7.16 (dd, *J* = 18.2, 7.6 Hz, 6H), 6.93 (d, *J* = 8.9 Hz, 2H). ¹³C NMR (101 MHz, DMSO- d_6) δ 170.7167.3, 163.2, 155.5, 154.9150.3, 145.7, 134.6, 132.8132.3, 129.9, 129.5, 129.2, 128.5128.0, 125.9, 125.6, 124.9122.7, 120.5, 119.1, 118.5. IR (KBr, (cm⁻¹)): 1741, 1587 (C=O), 1498 (C=C), 1060 (C–O); HRMS (ESI) calculated for C₃₄H₂₃NO₄ 510.1700[M+H]⁺, found 510.1709 [M+H]⁺.

2.2. Photoacid generation experiments

All 3HFs dissolved in acetonitrile were previously N_2 degassed. The photoacid generation progress was monitored via UV–visible absorption spectra. Rhodamine B (RhB) was used as a sensor of photoacid generation [23].

2.3. ESR experiments

ESR experiments were carried out using a Bruker A300 ESR spectrometer. The radicals were produced at room temperature under the 405 nm LED exposure and trapped by phenyl *N*-tert-butylnitrone (PBN) [24,25].

2.4. Cytotoxicity in a non-contact model

Five pieces (1 mm thick disc with 7 mm diameter) of polymer was prepared from the photopolymerization of the Bis-GMA/PEGDMA (70%/30%, wt/wt) blend initiated by the 3HFs (0.125%, wt), 3HFs/



Fig. 1. (a) Synthesis routes of the 3HFs; (b) Optimized geometry structures and molecular electrostatic potentials of 3HFs; (c) ¹³C NMR spectra of the 3HFs; (d) IR spectra of the 3HFs.

triethanolamine (TEOA) (0.125%/3.0%, wt/wt) and 3HFs/iodonium salt (ONI) (0.125%/1.0%, wt/wt) photoinitiating system under the 405 nm LED irradiation. For comparison, camphorquinon (CQ) was tested under the same experimental conditions. After being washed with 70% ethanol for 1 day, the polymer is soaked in culture medium for 7 days. HeLa cells were seeded in 96-well plates at a density of 1×10^{-4} cells per well and cultured for 24 h at 37 °C under a humidified atmosphere of 5% CO₂. After the attachment of HeLa cells, add the soaking solution to the culture medium and continue to culture the HeLa cells for 24 h. For each sample, the parallel control group were repeated five times. The viability of the HeLa cells was analyzed using the MTT cytotoxicity assay method. Finally, the optical density (OD) at 490 nm was read with a microplate reader. The cell viability (%) was calculated using the following equation [7,26].

Cell viability
$$= \frac{OD - OD_0}{OD_C - OD_0} \times 100\%$$

Where OD is the value of the experimental group, OD_C is the value for cells incubated with medium, and OD_0 is the value of the medium. The viability was tested in triplicate and the values were averaged.

3. Results and discussion

3.1. Synthesis

The synthesis of 3HF–OH was performed using the Algar– Flynn–Oyamada (AFO) method [27]. 3HF–S and 3HF–C were synthesized by replacing the 3-position hydroxyl group of 3HF–OH with benzenesulfonyl chloride and benzoyl chloride, respectively. Fig. 1a shows the synthesis routes. The ¹³C NMR spectra and infrared (IR) spectra are presented in Fig. 1c and d. The ¹³C NMR spectra of 3HFs show that there is only one peak in the 3HF–C spectra at chemical shift of about 163.87 ppm. The peak was attributed to the carboxylate group. The IR spectra of 3HFs show that there is only one peak in the 3HF–S spectra at 978 cm⁻¹. The peak was attributed to the sulfonate group.

The optimized geometry structures and molecular electrostatic potentials of 3HFs are shown in Fig. 1b. Their torsion angle is presented in Table S1. The triphenylamine structure on 3HF–S and 3HF–C will be subjected to torsion when benzenesulfonyl chloride and benzoyl chloride are used to replace the 3-position hydroxyl group on 3HF–OH. In addition, the benzene ring on the sulfonate and carboxylic acid ester and the flavonol molecule are not in a flat plane, which reduces the planarity



Fig. 2. (a) UV–Vis absorption spectra of the 3HFs in acetonitrile; (b) Calculated electron distributions of HOMOs and LUMOs for 3HFs. (c) Fluorescence spectra of the 3HFs in acetonitrile; (d) Photographs of 3HF–S in different solvents taken under excitation of a UV light (\sim 365 nm); (e) The fluorescent spectra of 3HF–S in methanol/water mixtures with different ratios.

Table 1

Absorption and fluorescence data of 3HFs in acetonitrile: maximum absorption wavelengths (λ_{max}), molar extinction coefficients (ϵ) at λ_{max} and at the emission wavelengths of the LEDs, maximum emission wavelengths (λ_{em}), Stokes shift and fluorescence quantum yields (Φ_f), Quantum yields for acid generation (Φ_H^+), irradiated at 405 nm, Chemical acid yields(Φ_{chem}), irradiated at 405 nm.

	λ_{\max} (nm)	$\varepsilon_{\rm max}$ (M ⁻¹ cm ⁻¹)	$\varepsilon_{405} (\mathrm{M}^{-1}\mathrm{cm}^{-1})$	$\varepsilon_{460} (\mathrm{M}^{-1} \mathrm{cm}^{-1})$	λ_{em} (nm)	Stokes shift (cm^{-1})	$\Phi_{\rm f}$ (%)	$\Phi_{\rm H}^+$	$\Phi_{\rm chem}$
3HF–OH	396	23752	22176	671	545	6711	18.24	-	-
3HF–S	386	23294	17448	672	549	6135	13.90	0.20	0.45
3HF–C	384	23012	16071	671	546	6173	15.23	0.002	0.27

of the overall molecule of 3HFs.

Solubility is an important for photoinitiator. Thus, the solubility of 3HFs in toluene, ethyl acetate (EA), tetrahydrofuran (THF), methanol (CH₃OH), acetonitrile (CH₃CN), dimethyl sulfoxide (DMSO), CH₃OH/H₂O (1:1 v/v), CH₃CN/H₂O (1:1 v/v), and DMSO/H₂O (1:1 v/v) are presented in Table S2. 3HF–S exhibited better solubility than 3HF–OH and 3HF–C in the tested solvents. Meanwhile, 3HF–S showed considerable solubility in the mixed solvents, which proved that 3HF–S is suitable for aqueous photoinitiated polymerization.

3.2. Light absorption and fluorescence properties

The ultraviolet–visible (UV–vis) absorption spectra of the studied 3HFs in CH_3CN are presented in Fig. 2a. The 3HFs are characterized by good light absorption properties in the 250–470 nm range. We found that these compounds are characterized by a high extinction coefficient in the 405 nm, and the absorption of 3HF–S and 3HF–C undergoes small

blue shift compared with the absorption of 3HF–OH. The absorption at approximately 400 nm is mainly due to the π – π * transition of the whole π -conjugated structure of 3HFs. The broad absorption range and visible light coverage are attributed to this large π -conjugated structure. Their extinction coefficients and the corresponding wavelengths are reported in Table 1.

The spatial electron distributions of the highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs) in the optimized ground states are depicted in Fig. 2b. The electrons of the HOMOs of 3HFs are basically delocalized on the triphenylamine molecules, while those of the LUMOs are mainly distributed at the other part of molecule except for the triphenylamine moiety. Both the HOMOs and the LUMOs are strongly delocalized all over the π system, clearly showing a π - π * lowest energy transition for 3HFs. The introduction of benzenesulfonyl chloride and benzoyl chloride in the 3HF–OH was found to increase the LUMO–HOMO energy gap, which is in accordance with the observed blueshift for λ_{max} .



Fig. 3. (a) Evolution of the absorption spectra of 3HF–S and Rhodamine B; (b) Evolution of the absorption spectra of 3HF–C and Rhodamine B; (in acetonitrile upon the 405 nm LED exposure, UV–vis spectra recorded at different irradiation times).

The fluorescence spectra of 3HFs in CH_3CN are presented in Fig. 2c, and the main data are listed in Table 1. In CH_3CN solvent, the fluorescence intensity of 3HF–S and 3HF–C was weaker than that of 3HF–OH. The decrease in the fluorescence intensity of 3HF–S and 3HF–C was partly due to the limitation of the ESIPT process of 3HF–OH. To further study the fluorescence behavior of 3HF–S, the fluorescence spectra in $CH_3OH/water$ mixtures (the maximum water contains 0.2% CH_3OH) with different water fractions (vol%) were studied, as shown in Fig. 2d and e. In CH₃OH/water mixtures, the initial fluorescence of 3HF–S in pure CH₃OH solution was very weak. Upon the increase of water fraction, the fluorescence intensity of 3HF–S gradually increased. The results suggested that the 3HF–S has aggregation-induced emission (AIE) characteristics.

3.3. Photoacid generation

The photoacid generation properties of 3HF-S and 3HF-C were tested using rhodamine B as an acid detector [23]. The mixture of 3HFs and RhB (1:2 molar ratio) was corradiated in CH₃CN and irradiated by 405 nm LED source. The results of the change of the absorption at approximately 400 nm indicated that photolysis took place in 3HF-S and 3HF-C under the irradiation, and the photolysis rate of 3HF-S is faster than that of 3HF-C, as shown in Fig. 3. The photostability of flavone derivatives has been investigated previously because of the following reasons: (1) 3HFs contain enol and enone structures. (2) Hydrogen atom transfer and electron transfer occur under LED illumination [14,22]. (3) The conjugate structure is broken, so the absorption is significantly reduced. As shown in Fig. 3, the intense increase in the absorbance at approximately 555 nm shows the production of acid accompanied with the photolysis with the increase of irradiation time. The absorption intensity of 3HF-S at 555 nm is higher than that of 3HF-C after the irradiation, which indicates that the photolysis of 3HF-S can produce strong acids. 3HF-S produced strong acids. Also, it accelerates the photolysis rate, which is one of the reasons that the photolysis rate of 3HF-S is faster than 3HF-C. Their quantum yields for acid generation (ΦH^+) and the chemical acid generation (Φ_{chem}) under the irradiation of 405 nm LEDs are gathered in Table 1.

The possible mechanism of this photoacid generation is shown in Scheme 2. It is believed that the mechanism of the 3HF–S is analogous to that of phenolic sulfonate photoacid generators [28], that is, the homolytic cleavage of the S–O bond to form a radical pair [3HFO• + \circ SO₂Ph], in the solvent cage, which then undergoes intramolecular coupling or cage escape. These radicals must escape from the solvent cage and undergo side reactions, such as react with water H₂O, for acid to be formed.

3.4. 3HFs as photoinitiators for free radical polymerization

Free radical photopolymerization (FRP) of tripropylene glycol diacrylate (TPGDA) was evaluated using 3HFs as photoinitiators under the 405 nm LED source and 460 nm LED source. The photopolymerization curves are shown in Fig. 4. Generally, the proportion of photoinitiator in photopolymerization is 1.0–3.0 wt%. Through acid generation experiments, the ester bonds in 3HF–S and 3HF–C are easily broken under light. It can be seen from Fig. S13 and Fig. S14 that the 3HF–S onecomponent systems can effectively initiate FRP of TPGDA, and the photoinitiator 3HF–S with low content of 0.125 wt% is sufficient for photopolymerization. It can be explained with these two factors: the AIE characteristics and light shielding [1]. At the same time, the low usage of 3HF–S further reduces the toxicity of the cured material.

Therefore, 3HFs as one-component photoinitiating system to initiate



Scheme 2. Proposed mechanism of photoacid generation.



Fig. 4. Photopolymerization profiles of TPGDA in the presence of 3HFs, 3HFs/TEOA, CQ and CQ/TEOA (3HFs/CQ: 0.125% wt; TEOA: 3.0% wt); (a and c) under the 405 nm LED; (b and d) under the 460 nm LED.



Fig. 5. (a) and (b) Photopolymerization profiles of TPGDA in the presence of 3HFs/ONI (0.125%/1.0% wt/wt) and CQ/ONI (0.125%/1.0% wt/wt); (c) and (d) Photopolymerization profiles of DGEBA in the presence of 3HFs/ONI (0.125%/1.0% wt/wt) and CQ/ONI (0.125%/1.0% wt/wt); (a and c) under the 405 nm LED; (b and d) under the 460 nm LED.

FRP of TPGDA were first evaluated, and the results were shown in Fig. 4a and b. Under the 405 nm LED light source, when irradiated for 180 s, the final conversions (FCs) of 3HF–S, 3HF–C, and 3HF–OH were

80%, 20%, and 3%, respectively. Under the 460 nm LED light source, when irradiated for 180 s, the FCs of 3HF–S, 3HF–C, and 3HF–OH were 71%, 3%, and 2%, respectively. The results showed that 3HF–S can be



Fig. 6. (a) Photopolymerization profiles of hydrogels [containing 70 wt% of PEGDMA (Mn = 600 Da) and 30 wt% of H_2O] in the presence of 3HFs, 3HFs/TEOA and 3HFs/ONI under the 405 nm LED; (b) and (c) photograph of 3D printed methacrylate resins with hexagonal grid structure; (d) and (e) photograph of 3D printed hydrogel with school badge structure; (c and e) under excitation of a UV light (~365 nm).



Fig. 7. ESR-ST spectra of radical generated in (a) 3HF–S, (b) 3HF–S/EDB (EDB is used to avoid the high polarity of TEOA [21]) and 3HF–S/ONI upon 405 nm LED exposure and trapped by PBN in tert-butylbenzene.



Fig. 8. The cytotoxicity of 3HFs in HeLa cells. (0) Blank control, (1) 3HF–OH/ TEOA, (2) 3HF–OH/ONI, (3) 3HF–S, (4) 3HF–S/TEOA, (5) 3HF–S/ONI, (6) 3HF–C, (7) 3HF–C/TEOA, (8) 3HF–C/ONI, (9) CQ, (10) CQ/TEOA, (11) CQ/ONI.

used as Novel Norrish type I photoinitiators. Furthermore, the photoinitiation activity of 3HF–S is the highest, which is consistent with its high acid generation activity and low O–S bond energy. However, 3HF–C and 3HF–OH have almost no initiation activity when they were used as Norrish I type photoinitiators.

Hydrogen donors are the most important as coinitiators among the Norrish type II photoinitiators. The effects of different amines including TEOA, triethylamine (TEA), ethyl 4-dimethylaminobenzoate (EDB), NPG, and morpholine (MP) on FRP were studied (Fig. S13). When TEOA, TEA, EDB, and MP are added, the polymerization rate is significantly increased, and using TEOA as the coinitiator has the highest polymerization rate. The photopolymerization of TPGDA with 3HF/TEOA as photoinitiator was tested to evaluate the ability of 3HFs as a Norrish type II photoinitiator. The results were shown in Fig. 4c and d. As a two-component system, 3HF/TEOA has shown higher photoinitiation activity than 3HFs as one-component photoinitiators. The addition of TEOA significantly accelerated the polymerization efficiency. Under the 405 nm and 460 nm LED light source, when irradiated for 20 s, the FCs of 3HF–S all can reach over 80%. At the same time, under the 405 nm LED light source, 3HF–S as one-component or two-component photoinitiating system, the polymerization rate is higher than the commercial initiator CQ.

3.5. 3HFs as photosensitizers for free radical and cationic photopolymerization

The molecular electrostatic potential (MEP) map offers a very crucial information in the form of local potentials on the total density surface of a molecule [29–31]. Fig. 1b reveals that the negative potentials of 3HFs are evenly localized on the carbonyl and ester moiety, which in turn provides a reaction site to interact with positive iodonium salts (ONIs) through electrostatic attraction. Therefore, the activity of 3HFs as ONI photosensitizers in the FRP of TPGDA and the cationic photopolymerization (CP) of bisphenol A diglycidyl ether (DGEBA) was investigated.

FRP experiments using two-component photoinitiating systems, which contain 3HF (0.125 wt%) and ONI (1.0 wt%), were also performed (Fig. 5a and Fig. 5b). The FC could reach up 85% for 3HFs/ONI (only 10% for CQ/ONI) under the 405 nm LED, when irradiation time

was 25 s. The order of polymerization rate was 3HF-S/ONI > 3HF-C/ONI > 3HF-OH/ONI > CQ/ONI under the 460 nm LED light sources. The addition of ONI significantly accelerated the polymerization rate because of its high activity.

Epoxy-based polymeric materials have diverse applications, such as adhesives, paints, coatings, and electronics. These materials have a set of unique properties, that is, low shrinkage, excellent chemical and corrosion resistance, and superior thermal properties. The photopolymerization of epoxy resin belongs to the CP initiated by ionium salts usually. The main absorption of the commonly used onium salt initiators (ONI and sulfonium salt) is concentrated in the ultraviolet region, which does not match the safe LED light source well. Thus, the photosensitizer for ONIs is very important in CP under the LED irradiation. The CP of DGEBA in the presence of the 3HFs (0.125% wt) and ONI (1.0% wt) was carried out under 405 nm and 460 nm LED light sources, respectively. The results are shown in Fig. 5c and d. Under the 405 nm LED light source, when irradiated for 150 s, the FCs of 3HF-S/ONI, 3HF-OH/ONI, 3HF-C/ONI, and CQ/ONI are 76%, 80%, 53%, and 30%, respectively. The order of polymerization rate was 3HF-OH/ONI > 3HF-S/ONI > 3HF-C/ONI > CO/ONI. Under the 460 nm LED light source, when irradiated for 180s, the FCs of 3HF-S/ONI, 3HF-OH/ONI, 3HF-C/ONI, and CQ/ONI are 65%, 46%, 45%, and 12%, respectively. The order of polymerization rate was 3HF-S/ONI > 3HF-C/ONI > 3HF-OH/ONI > CQ/ONI. The results show that the polymerization rate and the FCs of 3HFs in the CP system are higher than that of CQ. This shows that 3HF is also a new type of highly effective photosensitizer.

TPGDA methacrylate resins were used as polymerizable monomers in this study. The 3D printing structure obtained from methacrylate resins containing 3HF–S (0.125% wt), ONI (2.0% wt), and TEOA (1.0% wt) are shown in Fig. 6b and c. The hexagonal grid complex structure could be successfully printed with 3HF–S, and the structure has high precision. The printed model with photoinitiator 3HF–S is yellow (Fig. 6b), When the model is illuminated by UV light, its color turns blue (Fig. 6c). This result demonstrates that the 3HF–S is a good photoinitiator.

3.6. 3HFs as photoinitiators for photopolymerization of hydrogels

Hydrogels are three-dimensional (3D) networks formed by hydrophilic polymer chains with tunable physical and chemical properties. They have been widely used in biomedicine, soft electronics, sensors and actuators [32,33]. The 3HF–S has better solubility in mixed solvents, so it was selected to explore the photopolymerization of hydrogels. The hydrogels of PEGDMA in the presence of the 3HF–S was carried out under 405 nm LED light sources. It can be seen from Fig. 6a that the photoinitiator 3HF–S with low content of 0.042 wt% is totally enough for photopolymerization. When irradiated for 60 s, the FCs of 3HF–S, 3HF–S/TEOA, and 3HF–S/ONI were 33%, 75%, and 85%, respectively. The order of polymerization rate was 3HF–S/ONI > 3HF–S/TEOA > 3HF–S. The addition of H₂O significantly reduces the photoinitiator usage. It can be explained with the AIE characteristics. At the same time, the low usage of 3HF–S further reduces the toxicity of the hydrogels.

The efficiency of 3HF–S as photoinitiator was evaluated for 3D printing of hydrogels. The 3D printing structure obtained from aqueous formulations containing 3HF–S (0.125% wt), ONI (2.0% wt), and TEOA (1.0% wt) are shown in Fig. 6d and e. The school badge structure of hydrogels could be successfully 3D printed with 3HF–S and the stiffness of the structure was sufficient for further processing without breaking the structure. This plays an important role in the field of biomedicine.

3.7. Photochemical mechanism

The generated radicals 3HF–S, 3HF–S/EDB, and 3HF–S/ONI under 405 nm LED irradiation were observed by ESR spin-trapping experiments (Fig. 7). In the 3HF–S system, a triplet is observed, which may correspond to the benzenesulfonyl radical produced by the fracture of the ester bond. Moreover, ESR spectra of 3HF–S/EDB and 3HF–S/ONI systems are more complex than those of 3HF–S systems. This result shows that the 3HF–S/EDB system generates aminoalkyl radicals and that the 3HF–S/ONI system generates tolyl radicals [7,34].

Based on the aforementioned research, the photochemical mechanism was demonstrated in Scheme 3. As shown in Scheme 3A, in the onecomponent 3HF-S initiating system, ester bond cleavage occurs under light conditions, the generated 3HF radicals and benzenesulfonyl radicals are in the solvent cage, and then, the free radicals escape from the cage and initiate FRP. In the two-component 3HF-S/TEOA initiating system, as shown in Scheme 3B, 3HF-S can undergo classic enone tautomer conversion under light conditions, generating electron transfer with TEOA, and then, the aminoalkyl radicals initiate FRP. At the same time as shown in Scheme 3A, 3HF free radicals and benzenesulfonyl free radicals can also undergo electron transfer with TEOA and generate aminoalkyl radicals to initiate FRP. In the two-component 3HF-S/ONI initiating system, as shown in Scheme 3C, 3HF-S is excited under light conditions and then undergoes electron transfer with ONI to generate a free radical cation and an unstable onium salt free radical. Unstable onium salt radicals generate tolyl radicals to initiate FRP. At the same time, in the process of electron transfer between 3HF-S and ONI, super acid and free radical cation can also be generated to initiate CP.

3.8. Cytotoxicity of the photocured films

To evaluate the biocompatibility of the photocured films, the in vitro cytotoxicity on HeLa cells was measured by using MTT assay. In this study, the typical dental resin system bisphenol A-glycidyl methacrylate (bis-GMA)/poly (ethylene glycol) dimethacrylate (PEGDMA) was used as the benchmark monomer. The cytotoxicity assays of the photocured films are shown in Fig. 8. The cell viability of the cured films with 3HF–S, 3HF–C, and CQ is sustained more than 80%, whereas the cell viability of the cured films with 3HF–OH is less than 80%. This is because 3HF–OH has poor solubility, which is caused by a reduction of *N*-methyl-2-pyrrolidone added to the cured sample. Therefore, the 3HF–S and 3HF–C have a great potential in field of biomaterials.

4. Conclusions

In summary, the novel LED photoinitiator 3HFs were synthesized via the method of Algar-Flynn-Oyamada and a substitution reaction. The photoinitiation abilities of 3HFs have been investigated using safe longwavelength LED soft light sources. The high extinction coefficient and AIE characteristics of 3HF–S were observed, which proved that reducing the photoinitiator usage can effectively progress the photopolymerization activity. At the same time, the low usage of 3HF-S further reduces the toxicity of the cured material. 3HF-S can be used as Norrish I type photoinitiators. Furthermore, the photoinitiation activity of 3HF-S is the highest, which is consistent with its high acid generation activity and low O-S bond energy. The polymerization rate and FCs of 3HFs in the CP system are higher than that of CQ. This shows that 3HF is also a new type of highly effective photosensitizer. Moreover, the use of MTT method confirmed the lower toxicity for the final photopolymer provided. Finally, we were able to come up with a new highly efficient and safe photoinitiator that will play an important role in the field of biocompatible polymers.

CRediT authorship contribution statement

Jian You: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. Ding Cao: Resources. Tianyu Hu: Investigation. Yaoyao Ye: Investigation. Xiaoqin Jia: Investigation. Hui Li: Investigation. Xiaotong Hu: Investigation. Yingying Dong: Investigation. Yufan Ma: Investigation. Tao Wang: Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition.



Scheme 3. photochemical mechanisms of the generation of radicals in (A) 3HF-S, (B) 3HF-S/TEOA and (C) 3HF-S/ONI.

declaration of competing interest

The authors declare no competing financial interest.

Acknowledgements

We acknowledge the Beijing Natural Science Foundation (2202035) and the State Key Laboratory of Optoelectronic Materials and Technologies (Sun Yat-sen University) (OEMT-2018-KF-12) for financial support. We also thank the Beijing University of Chemical Technology CHEMCLOUDCOMPUTING Platform for support with calculations.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dyepig.2020.108865.

References

- Li J, Hao Y, Zhong M, Tang L, Nie J, Zhu X. Synthesis of furan derivative as LED light photoinitiator: one-pot, low usage, photobleaching for light color 3D printing. Dyes Pigments 2019;165:467–73. https://doi.org/10.1016/j.dyepig.2019.03.011.
- [2] Liu R, Mabury SA. Photoinitiators in breast milk from United States donors: occurrence and implications for exposure in infants. Environ Sci Technol Lett 2019; 6(12):702–7. https://doi.org/10.1021/acs.estlett.9b00626.
- [3] Kandirmaz EA, Gençoğlu EN, Apohan NK. The synthesis of new type II polymeric photoinitiator (thioxantone) via atom transfer radical polymerization and their curing and migration studies. Macromol Res 2019;27(8):756–63. https://doi.org/ 10.1007/s13233-019-7107-3.
- [4] Kreutzer J, Kaya K, Yagci Y. Poly (propylene oxide)-thioxanthone as onecomponent Type II polymeric photoinitiator for free radical polymerization with low migration behavior. Eur Polym J 2017;95:71–81. https://doi.org/10.1016/j. eurpolymj.2017.07.030.
- [5] Wu Q, Tang K, Xiong Y, Yang J, Tang H. High-Performance and low migration onecomponent thioxanthone visible light photoinitiators. Macromol Chem Phys 2017; 1600484(6):218. https://doi.org/10.1002/macp.201600484.
- [6] Kandirmaz EA, Apohan NK, Gencoglu EN. Preparation of novel thioxanthone based polymeric photoinitiator for flexographic varnish and determination of their migration behaviour. Prog Org Coating 2018:36–43. https://doi.org/10.1016/j. porgcoat.2018.02.012.
- [7] Zhao J, Lalevée J, Lu H, MacQueen R, Kable SH, Schmidt TW, Stenzel MH, Xiao P. A new role of curcumin: as a multicolor photoinitiator for polymer fabrication under household UV to red LED bulbs. Polym Chem 2015;6(28):5053–61. https:// doi.org/10.1039/C5PY00661A.
- [8] Al Mousawi M, Garra P, Schmitt M, Toufaily J, Hamieh T, Graff B, Fouassier JP, Dumur F, Lalevée J. 3-Hydroxyflavone and N-phenylglycine in high performance photoinitiating systems for 3D printing and photocomposites synthesis. Macromolecules 2018;51:4633–41. https://doi.org/10.1021/acs. macromol.8b00979.
- [9] Rao YJ, Sowjanya T, Thirupathi G, Murthy NYS, Kotapalli SS. Synthesis and biological evaluation of novel flavone/triazole/benzimidazole hybrids and flavone/isoxazole-annulated heterocycles as antiproliferative and antimycobacterial agents. Mol Divers 2018;22(4):803–14. https://doi.org/ 10.1007/s11030-018-9833-4.
- [10] Balasuriya N, Rupasinghe HPV. Antihypertensive properties of flavonoid-rich apple peel extract. Food Chemistry 2012;135:2320–5. https://doi.org/10.1016/j. foodchem.2012.07.023.
- [11] Kawai M, Hirano T, Higa S, Arimitsu J, Maruta M, Kuwahara Y, Ohkawara T, Hagihara K, Yamadori T, Shima Y, Kawase AOI, Tanaka T. Flavonoids and related compounds as anti-allergic substances. Allergol Int 2007;56:113–23. https://doi. org/10.2332/allergolint, R-06-135.
- [12] Orhan DD, Özçelik B, Özgen S, Ergun F. Antibacterial, antifungal, and antiviral activities of some flavonoids. Microbiol Res 2010;165:496–504. https://doi.org/ 10.1016/j.micres.2009.09.002.
- [13] Forbes AM, Lin H, Meadows GG, Meier GP. Synthesis and anticancer activity of new flavonoid analogs and inconsistencies in assays related to proliferation and viability measurements. Int J Oncol 2014;45:831–42. https://doi.org/10.3892/ ijo.2014.2452.
- [14] Liu B, Luo Z, Si S, Zhou X, Pan C, Wang L. A photostable triphenylamine-based flavonoid dye: solvatochromism, aggregation-induced emission enhancement, fabrication of organic nanodots, and cell imaging applications. Dyes Pigments 2017;142:32–8. https://doi.org/10.1016/j.dyepig.2017.03.023.

- [15] Dziuba D, Postupalenko VY, Spadafora M, Klymchenko AS, Guérineau V, Mély Y, Benhida R, Burger A. A universal nucleoside with strong two-band switchable fluorescence and sensitivity to the environment for investigating DNA interactions. J Am Chem Soc 2012;134(24):10209–13. https://doi.org/10.1021/ja3030388.
- [16] Yushchenko DA, Fauerbach JA, Thirunavukkuarasu S, Jares-Erijman EA, Jovin TM. Fluorescent ratiometric MFC probe sensitive to early stages of α-synuclein aggregation. J Am Chem Soc 2010;132(23):7860–1. https://doi.org/10.1021/ ja102838n.
- [17] Klymchenko AS, Demchenko AP. Electrochromic modulation of excited-state intramolecular proton transfer: the new principle in design of fluorescence sensors. J Am Chem Soc 2002;124(41):12372–9. https://doi.org/10.1021/ja027669l.
- [18] Sengupta PK, Kasha M. Excited state proton-transfer spectroscopy of 3-hydroxyflavone and quercetin. Chem Phys Lett 1979;68:382–5. https://doi.org/10.1016/ 0009-2614(79)87221-8.
- [19] McMorrow D, Kasha M. Intramolecular excited-state proton transfer in 3-hydroxyflavone. Hydrogen-bonding solvent perturbations. J Phys Chem 1984;88: 2235–43. https://doi.org/10.1021/j150655a012.
- [20] Ameer-Beg S, Ormson SM, Brown RG, Matousek P, Towrie M, Nibbering ETJ, Foggi P, Neuwahl FVR. Ultrafast measurements of excited state intramolecular proton transfer (ESIPT) in room temperature solutions of 3-hydroxyflavone and derivatives. J Phys Chem 2001;105:3709–18. https://doi.org/10.1021/jp0031101.
- [21] Tehfe M-A, Dumur F, Xiao P, Graff B, Morlet-Savary F, Fouassier JP, Gigmes D, Lalevée J. New chromone based photoinitiators for polymerization reactions under visible light. Polym Chem 2013;4:4234–44. https://doi.org/10.1039/ C3PV00536D.
- [22] You J, Fu H, Zhao D, Hu T, Nie J, Wang T. Flavonol dyes with different substituents in photopolymerization. J Photochem Photobiol Chem 2020. https://doi.org/ 10.1016/j.jphotochem.2019.112097.
- [23] Jin M, Zhou R, Yu M, Pan H, Wan D. D-π-a-type oxime sulfonate photoacid generators for cationic polymerization under UV-visible LED irradiation. J Polym Sci Polym Chem 2018;56(11):1146-54. https://doi.org/10.1002/pola.28996.
- [24] Ouari O, Hardy M, Karoui H, Tordo P. Recent developments and applications of the coupled EPR/Spin trapping technique (EPR/ST). Electron Paramagnetic Resonance 2011;22:1–40. https://doi.org/10.1039/9781849730877-00001.
- [25] Atherton NM, Davies MJ, Gilbert BC, Tordo P. Spin-trapping: recent developments and applications. Electron paramagnetic resonance 1998;16:116–44. https://doi. org/10.1039/9781847553539-00116.
- [26] Wei M, Gao Y, Jiang S, Nie J, Sun F. Design of photoinitiator-functionalized hydrophilic nanogels with uniform size and excellent biocompatibility. Polym Chem 2019;10(22):2812–21. https://doi.org/10.1039/c9py00054b.
- [27] Algar J, Flynn JP. A new method for the synthesis of flavonols. 1934.
- [28] Andraos J, Barclay GG, Medeiros DR, Baldovi MV, Scaiano JC, Sinta R. Model studies on the photochemistry of phenolic sulfonate photoacid generators. Chem Mater 1998;10(6):1694–9. https://doi.org/10.1021/cm980052b.
- [29] Muhammad S, Xu H, Su Z, Fukuda K, Kishi R, Shigeta Y, Nakano M. A new type of organic-inorganic hybrid NLO-phore with large off-diagonal first hyperpolarizability tensors: a two-dimensional approach. Dalton Trans 2013;42 (42):15053–62. https://doi.org/10.1039/C3DT51331A.
- [30] Muhammad S, Al-Sehemi AG, Su Z, Xu H, Irfan A, Chaudhry AR. First principles study for the key electronic, optical and nonlinear optical properties of novel donor-acceptor chalcones. J Mol Graph Model 2017;72:58–69. https://doi.org/ 10.1016/j.jmgm.2016.12.009.
- [31] Xue T, Wang T, Nie J. Unveiling the electronic effect of substituent on sensitized photopolymerization: an experimental and theoretical investigation. Journal of Photochemistry and Photobiology A-chemistry. https://doi.org/10.1016/j.jph otochem.2020.112551; 2020.
- [32] Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science 2017: 356. https://doi.org/10.1126/science.aaf3627. eaaf3627.
- [33] Wang J, Stanic S, Altun AA, Schwentenwein M, Dietliker K, Jin L, Stampfl J, Baudis S, Liska R, Grutzmacher H. A highly efficient waterborne photoinitiator for visible-light-induced three-dimensional printing of hydrogels. Chem Commun 2018;54(8):920–3. https://doi.org/10.1039/C7CC09313F.
- [34] Han W, Fu H, Xue T, Liu T, Wang Y, Wang T. Facilely prepared blue-green light sensitive curcuminoids with excellent bleaching properties as high performance photosensitizers in cationic and free radical photopolymerization. Polym Chem 2018;9(14):1787–98. https://doi.org/10.1039/C8PY00166A.