

New generation of highly efficient long-wavelength photoinitiators for dental restoratives: From research to application

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Introduction

Current state-of-the-art dental composites^{1,2} are limited to layer-by-layer application due to the limited penetration depth of used blue light. Usually, the dental composite consists of about 60-80 wt% inorganic fillers and an organic matrix, comprising of photomonomers which are cured by light via the excitation of a photoinitiator (PI)^{3,4}. The most commonly used initiating system for photopolymerizable dental implants is a Type II PI consisting of camphorquinone (CQ) and ethyl 4-dimethylaminobenzoate (DMAB). However, this bimolecular PI-system exhibits numerous significant drawbacks such as low reactivity and stability, especially in water-based formulations.⁵ The demand for an appropriate PI for visible light curing⁶ is high not only for dental restoratives, but also in many other areas such as in the fields of laser-induced 3D printing and regenerative medicine. By enabling curing at wavelengths above 400 nm, the light can penetrate deeper into the composite and start a polymerization reaction because most components of the organic matrix do not absorb in this light region. Moreover, a PI that photobleaches during the photopolymerization would be beneficial and also lead to an increase in curing depth. The research towards long-wavelength PIs in our group has mainly focused on phosphorous compounds⁷, e.g. mono- and bisacylphosphine oxides, and germanium compounds^{8,9} such as acylgermanes. Unfortunately, the absorption for the developed phosphor-PIs tails out at roughly 420 nm. This makes those PIs unsuitable for dental medicine since commercial LED-dental lamps are adapted to the absorption spectrum of CQ and emit in the visible light region between about 420 and 500 nm. However, with the development of germanium-based PIs **1** and **2** (Figure 1), modern dental filling materials were improved regarding their reactivity and stability in acidic and aqueous media. Their achievable curing depth has also been greatly enhanced.

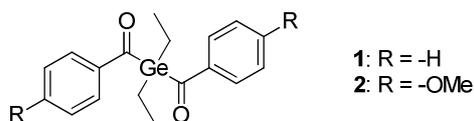


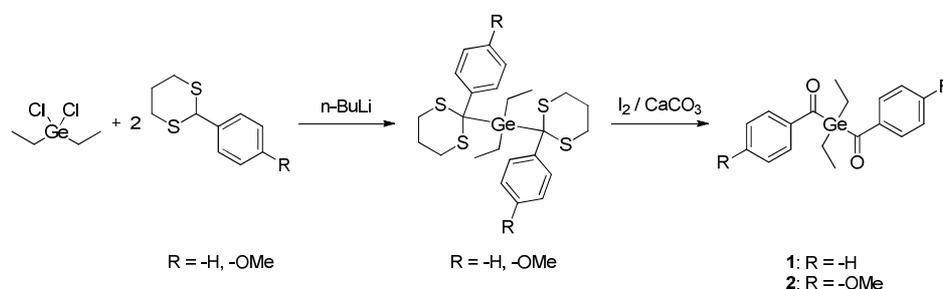
Figure 1: Acylgermanes **1** and **2**

The pathway of the germanium PI from research onto the commercial product Ivocerin[®] from Ivoclar Vivadent AG is elucidated in this paper. The general synthesis of the novel germanium PIs is described and UV-VIS absorption and photo-DSC studies of **1** show the absorption characteristics and photoinitiating activity under long-wavelength irradiation compared with phosphorous-based PIs and a Type II CQ/DMAB system.¹⁰ Storage stability tests under acidic conditions were conducted and steady state photolysis gave an idea about quantum yields and the photobleaching effect of **1**. The first tests on visible light curing of dental composites showed high potential for the germanium initiator **1**.¹¹ Direct photophysical experiments such as time-resolved electron paramagnetic resonance spectroscopy (TR-EPR) and chemically induced dynamic nuclear polarization (CIDNP) gave insights about the mechanistic behaviour of **1** upon irradiation.¹² The reactivity of germanium radicals was investigated as well and compared to benzoyl and phosphorous radicals. After the conduction of mechanical and clinical tests, a bulk fill dental composite (Tetric EvoCeram Bulk Fill) was developed by the company Ivoclar Vivadent AG and cleared for the market.

Results and Discussion

Synthesis

The synthesis of compounds **1** and **2** was carried out following the dithiane route¹³ which paves the way for a wide variety of derivatives by introducing different aromatic 1,3-dithianes (Scheme 1). After reacting the 1,3-dithianes with *n*-BuLi at low temperature, the corresponding carbanions are formed and react very efficiently with organic dichlorogermanium compounds (e.g., diethylgermanium dichloride) under the formation of the intermediate dithiane germanium compound. After the second reaction step, the oxidative cleavage of the protecting group with CaCO₃ and Iodine, the desired PIs were isolated in satisfactory yields (**1**, 25 %; **2**, 64%).¹⁴



Scheme 1: Synthesis of germanium PIs **1** and **2**.

UV-VIS and Photo-DSC studies

After the successful synthesis of the germanium PIs, the first studies on absorption and photoreactivity were performed on **1**.¹⁰

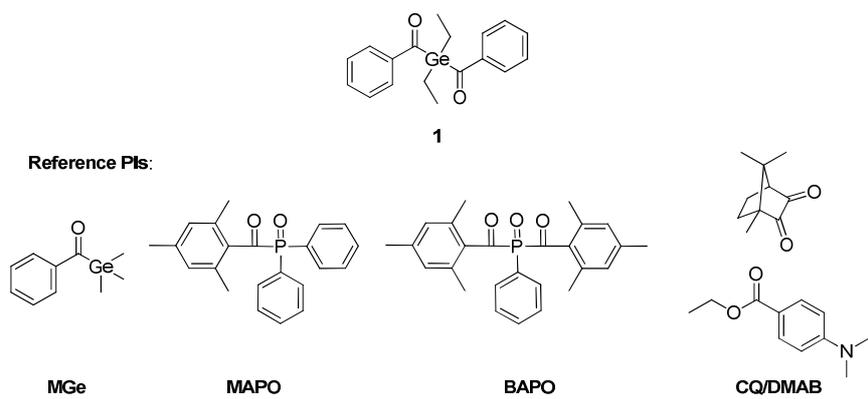


Figure 2: Germanium PI **1** and reference PIs **MGe**, **MAPO**, **BAPO** and **CQ/DMAB**.

UV-VIS absorption spectra of **1** and four reference PIs (Figure 2) were recorded in acetonitrile. It can be easily observed how acylgermanes **MGe** and **1** exhibit a red-shift of the absorption maximum of the $n-\pi^*$ transition over 400 nm (Figure 3). The red-shift of compound **1** is 20 nm and 50 nm compared to both $n-\pi^*$ maxima of **BAPO**. The extinction coefficient ϵ of **2** ($21 \text{ L mol}^{-1} \text{ cm}^{-1}$) is in the same order of magnitude as ϵ of **CQ** at its absorption maximum of 468 nm ($44 \text{ L mol}^{-1} \text{ cm}^{-1}$).

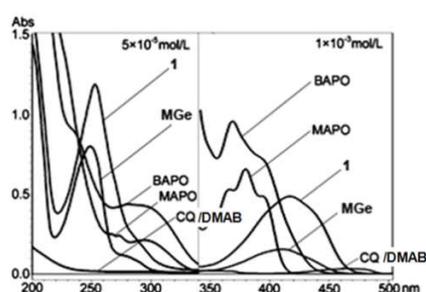


Figure 3: UV-VIS absorption of **1** and reference PIs.

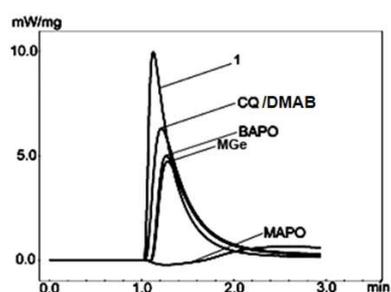


Figure 4: Photo-DSC experiments in dental resin.

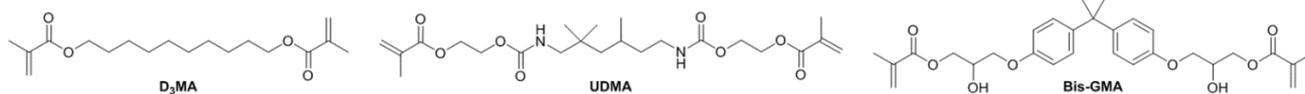


Figure 5: Monomers for organic matrix of dental composites.

For the photo-DSC experiments (Figure 4), $22 \mu\text{mol/g}$ of PI was mixed with a standard organic matrix for dental composites (**D₃MA/UDMA/Bis-GMA** 1:1:1, Figure 5). The measurements were carried out under a continuous nitrogen flow with a blue LED dental lamp provided by Ivoclar Vivadent AG (Bluephase C8, 430-490 nm) and the resulting photo-DSC curves are displayed in Figure 4. As expected, the phosphorous-based PI **MAPO** performed very poorly under the used conditions. The germanium-based PI **MGe** shows similar reactivity as **BAPO** and the commercial **CQ/DMAB** PI system, but by using the bisacylgermanium compound **1** a very good photopolymerization under visible light conditions can be achieved, even better than with the **CQ/DMAB** system.

Steady State Photolysis and Photobleaching

For the steady state photolysis (SSP), two tested PIs (**1** and **BAPO**) were dissolved in acetonitrile to show an initial absorption of 0.5 at 365 nm. The solutions were irradiated with an LED light source

(365 nm; Exfo Omnicure 2000) at an intensity of 1 W/cm^2 . UV-VIS measurements were conducted after set time intervals to determine the photodecomposition of the PIs (Figure 6 and Figure 7). Additionally, the photobleaching effect could be examined during those experiments since the photolysis products of **1** do not show absorbance in the spectral range of visible light.

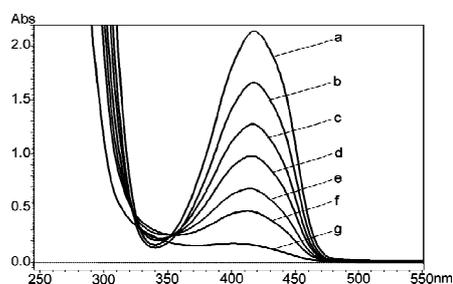


Figure 6: SSP of **1** after: 0 h (a); 1 h (b); 2 h (c); 3 h (d); 4 h (e); 5 h (f); 6 h (g).

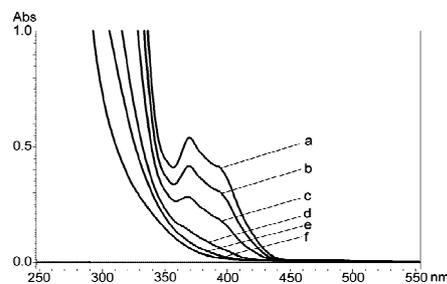


Figure 7: SSP of **BAPO** after: 0 h (a); 1 h (b); 2 h (c); 3 h (d); 4 h (e); 5 h (f).

The quantum yields of decomposition (Φ_D) were determined with the help of chemical actinometry.¹⁵ The chemical actinometer used was o-nitrobenzaldehyde ($\Phi_D = 0.5 \text{ mol einstein}^{-1}$; 310-400 nm) and an LED light source (365 nm) provided monochromatic irradiation.¹⁶ The evaluated Φ_D for **1** is $0.85 \text{ mol einstein}^{-1}$. This shows that PI **1** is significantly more effective than for example BAPO with Φ_D of $0.59 \text{ mol einstein}^{-1}$.¹⁰

Mechanistic investigations

In principle, Type I PIs such as **1** undergo different mechanisms (e.g. α -cleavage or H-abstraction) during the initiation process which result in the formation of radicals. Those radicals can be detected by time-resolved EPR spectroscopy and ^1H CIDNP technique.

Time-resolved EPR experiment

The measured polarized EPR spectrum of PI **1** (Figure 8) is created by laser-flash photolysis (Nd:YAG 355 nm) in toluene after 250 ns. Two overlapping signals for the radicals, the benzoyl-radical (**blue**; unresolved narrow signal; $g = 2.000$) and the germyl-radical (**green**; quintet 1:4:6:4:1; $g = 2.006$), were observed in emission (triplet mechanism).¹²

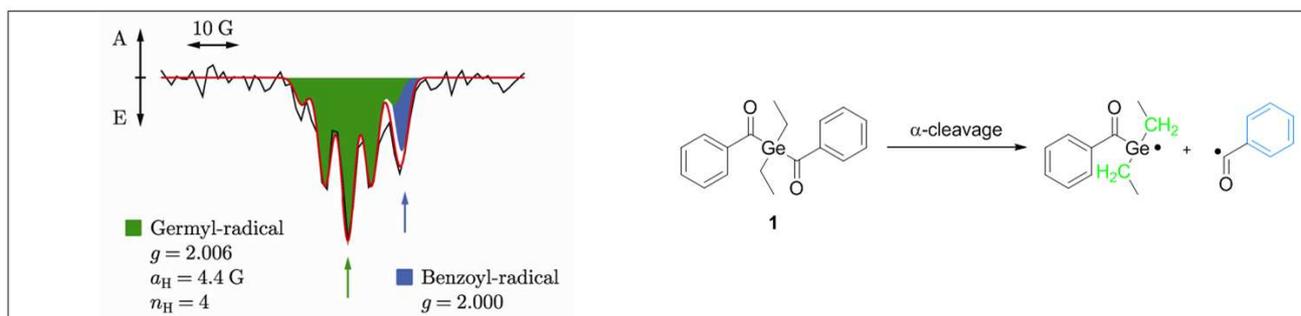


Figure 8: TR-EPR spectrum of **1**.

^1H CIDNP

The ^1H NMR spectrum of the PI **1** was recorded in d_8 -toluene and additionally two CIDNP spectra were measured 1 and 20 μs after the laser flash, respectively (Figure 9).¹² When comparing the ^1H NMR and CIDNP experiments, the radical recombination products (**3-6**) of the photolysis reaction of **1** can be observed and a reaction mechanism can be proposed (Figure 10).

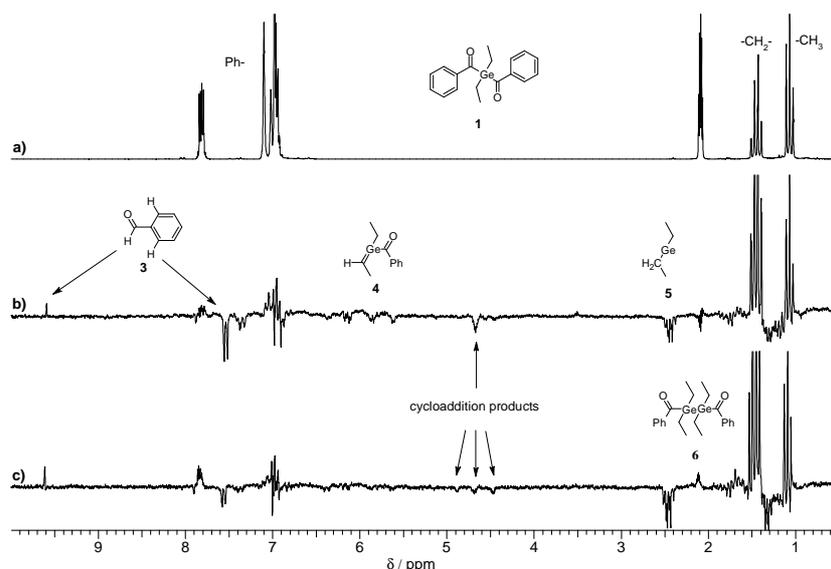


Figure 9: ^1H NMR (a), 1 μs (b) and 20 μs (c) CIDNP spectra of **1**.

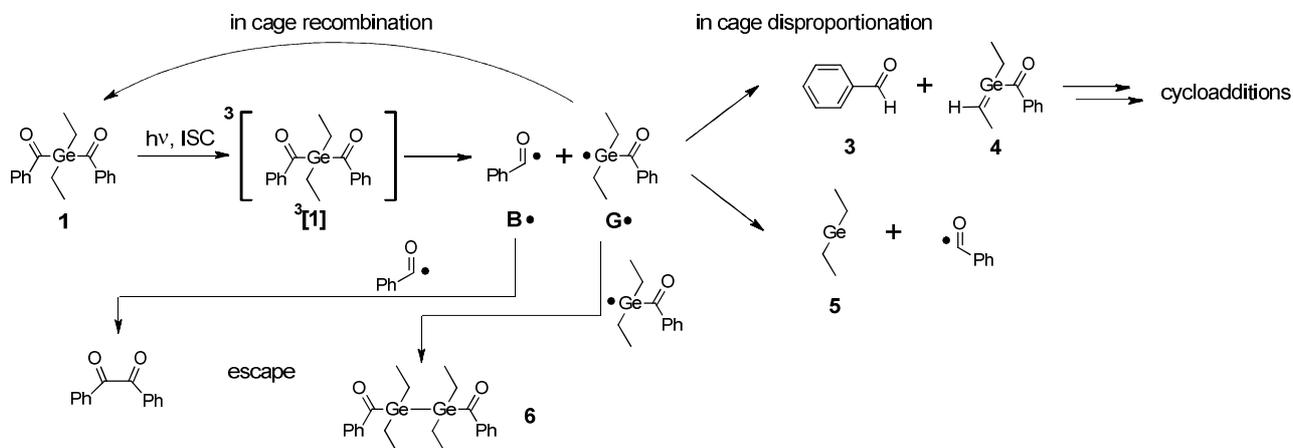


Figure 10: Proposed reaction mechanism following α -cleavage for PI **1**.

Fast intersystem crossing (ISC) from the excited singlet to the excited triplet state $^3[1]$ is implied by the proposed mechanism and α -cleavage leads to the two detected radicals, the benzoyl- and the germyl-radical.

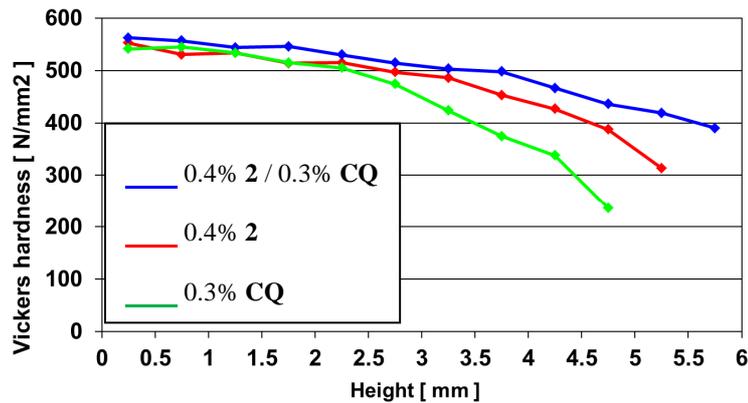


Figure 13: Vickers hardness profiles of composites with different PIs.

The novel PI 2 has been incorporated into a state-of-the-art dental composite material, resulting in a bulk fill product (Tetric EvoCeram Bulk Fill) developed by Ivoclar Vivadent AG. Compared to previous dental composites, the new bulk fill composite increases the light-curing depth from 2 mm up to 4 mm (Figure 14).

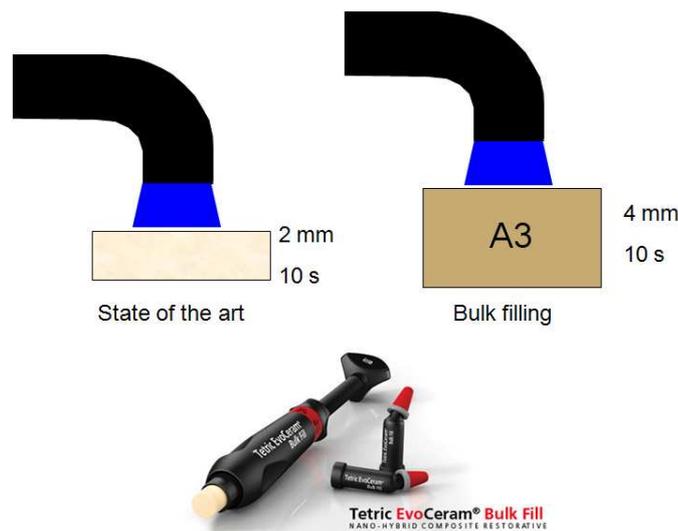


Figure 14: Tetric EvoCeram Bulk Fill by Ivoclar Vivadent AG.

Toxicity of Ivocerin[®]

While inorganic germanium compounds are usually toxic, organic germanium compounds are often characterized by very low toxicity. The LD₅₀ value of tetraalkylgermanes ranges between 3000 and 5000 mg/kg, for example.¹⁷

The cytotoxicity (XTT₅₀ value) of Ivocerin[®] was investigated by means of an XTT assay. The photo-initiator was found to be non-cytotoxic.¹⁸ Moreover, two mutagenicity tests were conducted. Both the Ames test (in vitro)¹⁹ and the Mouse Micronucleus Assay (in vivo)²⁰ did not reveal any mutagenic effects of Ivocerin[®].

Conclusion

A new class of germanium PIs has been synthesized and investigated, leading to the commercialization of the product Ivocerin[®] (**2**) in dental composites. UV-VIS absorption experiments revealed the desired bathochromic shift of the PIs (**1**: $\lambda_{\text{max}} = 418.5 \text{ nm}$) and photo-DSC studies proved the high photoreactivity of the acylgermanes compared to state-of-the-art PIs. Moreover, with the help of steady state photolysis, the photobleaching effect of PIs **1** and **2** was elucidated under practical conditions enabling higher curing depths. Following those promising results for visible light curing, time-resolved EPR and CIDNP experiments were conducted to detect the formed radicals and radical recombination products during photolysis and to propose a reaction pattern for the PIs **1** and **2**. The first step of photolysis was found to be the α -cleavage of the germanium-carbonyl-bond which gives a benzoyl radical and a benzoyldiethylgermanium-radical. Significant follow-up products such as benzaldehyde **3** and germane **4** were found with the CIDNP technique. The company Ivoclar Vivadent AG concluded the basic studies on the germanium-based PIs and extended the study with additional mechanical and clinical tests of dental composites. As a result of the satisfying studies, the PI **2** was introduced to the market under the trade name Ivocerin[®] and a dental composite with improved curing depth was developed (Tetric EvoCeram Bulk Fill) using a combination of CQ/DMAB and Ivocerin[®] as PI system.

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