

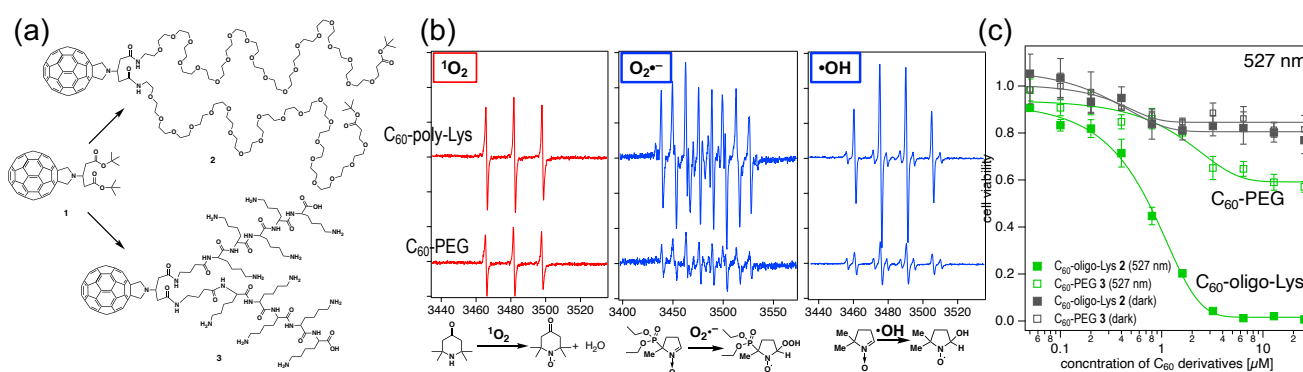
Visible light-induced reactive oxygen generation by water-soluble C₆₀ derivatives

Lorenzo Persi,¹ Barbara Ventura,² and Yoko Yamakoshi¹

¹Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 3, CH 8093 Zürich, Switzerland; ²Instituto per la Sintesi Organica e la Foreoreattiva, Consiglio Nazionale delle Ricerche (ISOF-CNR), 40129 Bologna, Italy
yamakoshi@org.chem.ethz.ch

Taking advantage of the efficient photosensitivity of C₆₀ under visible light irradiation,^[1] we have been developing water-soluble C₆₀ derivatives based on the versatile fulleropyrrolidine precursor **1**.^[2] In our initial approach, we introduced biocompatible polyethylene glycol (PEG), affording the highly water-soluble derivative C₆₀-PEG **2**, which forms aggregates on the 10 nm scale.^[3]

Recently, we developed C₆₀-oligopeptide conjugates through solid phase peptide synthesis.^[4] Among the successfully prepared C₆₀-peptides, C₆₀-oligo-Lys **3** (Fig. a) revealed significantly higher water-solubility and minimal aggregation, as observed by DLS. This behavior is presumably due to electrostatic repulsion between the positively charged, at least partially protonated Lys residues. The singlet oxygen (¹O₂) generation of C₆₀-oligo-Lys **3** was measured by both ESR spin-trapping method and phosphorescence measurements, revealing enhanced ¹O₂ generation compared with the control C₆₀-PEG derivative **2**. This improvement is likely related to the lower degree of aggregation of C₆₀-oligo-Lys **3** in comparison to C₆₀-PEG **2**. Interestingly, more toxic reactive oxygen species (O₂^{•-} and •OH) were efficiently produced by C₆₀-oligo-Lys **3** *via* the electron transfer pathway (Fig. b). In photocytotoxicity assay, C₆₀-PEG **2** showed no significant activity, whereas C₆₀-oligo-Lys **3** exhibited strong phototoxicity only under light irradiation (Fig. c), consistent with its enhanced ROS generation. In addition, the positively charged Lys residues in C₆₀-oligo-Lys **3** may promote interaction of the C₆₀ photosensitizer with generally negatively charged cell membranes. Building on C₆₀-oligo-Lys **3** as a core structure, we have further developed enzyme-reactive photosensitizers.^[5]



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