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Host-Guest Complexation of Amphiphilic Molecules at the Air-Water Interface Prevents Oxidation by Hydroxyl Radicals and Singlet Oxygen

Wen-Chao Geng,[+] Dongmei Zhang,[+] Chu Gong, Zhihao Li, Kevin M. Barraza, J. L. Beauchamp, Dong-Sheng Guo* and Xinxing Zhang**

Abstract: *The paradox of antioxidants is that they protect other more valuable molecules by sacrificial reactions with oxidizers. Their consequential loss in efficacy imposes great challenges to both living organisms and the food industry. Here we show that the host-guest complexation of the carefully designed positively charged amphiphilic guanidinocalix[5]arene pentadodecyl ether (GC5A-12C) and negatively charged oleic acid (OA), a well-known cell membrane antioxidant, prevents the oxidation of the complex monolayers at the air-water interface from two potent oxidizers hydroxyl radicals (OH) and singlet delta oxygen (SDO). OH is generated from the gas phase and attacks from the top of the monolayer, while SDO is generated inside the monolayer and attacks amphiphiles from a lateral direction. Field-induced droplet ionization mass spectrometry results have demonstrated that the host-guest complexation is able to achieve steric shielding and to prevent both types of oxidation as a result of the tight and "sleeved in" physical arrangement, rather than the chemical reactivity, of the complexes.*

Oxidation and antioxidation is an ongoing and never-ending tug of war both in living organisms[1] and in the food industry.[2] Being strong reducing agents in nature, antioxidants are self-sacrificial, which in turn imposes great challenges to their own preservation and slow or targeted release. Some efforts have been spent to design and synthesize organic/inorganic nano-particulate, porous, or polymeric supports for the encapsulation of antioxidants in order to achieve longer preservation and controlled delivery.[3] However, all of the studies to date involve the incorporation of many antioxidant molecules into a single large support (a nanoparticle or a polymer macromolecule). Here we aim to protect oleic acid (OA), a well-known cell membrane antioxidant[4] and fluidifier,[5] in a precise manner by adopting host-guest interactions, which promise to deliver the "one-on-one escort" of OA while shielding it from oxidation.

Host-guest motifs are composed of a discrete macrocyclic host with a cavity that selectively binds with guest molecules via non-covalent interactions.[6] One particular class of macrocycles, calix[*n*]arene (C*n*A, *n* = 4, 5, 6, 8),[7] has been regarded as the "supramolecules of the third generation"[8] after crown ether and cyclodextrin due to the large varieties of applications they can offer. More recently, by tuning the photochemical and photophysical properties, the C*n*A·guest complexation has been utilized in much more complex environments such as bioimaging, biomedication, and early diagnosis of cancer.[9] In this study, the complex of negatively charged OA and positively charged guanidinium-modified calix[5]arene pentadodecyl ether (GC5A-12C, denoted as G for short) is chosen for the proof-of-principle protection of antioxidants by host-guest complexation. G is carefully designed in terms of cavity size and chain length to host OA. With five potential positive charges, a list of GC5A·5HCl hosts decorated with different hydrocarbon chains have exhibited excellent complementary binding with negative charged guests.[9a, c] The long pentadodecyl hydrocarbon chains are decorated to GC5A in this study to pair with OA and to make the molecule amphiphilic for the delivery of a monolayer of molecules to the air-water interfaces, a frontier that can easily engage oxidation both *in vivo* and in the environment.[10] The structures of all the molecules studied are presented in Figure 1. Two potent oxidizers, hydroxyl radical (OH) and singlet delta oxygen ($^1O_2$, $^1\Delta_g$, SDO), are selected to represent the strong oxidizing agents that a molecule might encounter both *in vivo* and in contact with the atmosphere.[11] OH is generated in the gas phase to study the oxidation of the monolayer at the air-water interface from the top (Figure 1a), and SDO is generated in the monolayer by a lipophilic photosensitizer (PS) temoporfin (T) to study oxidation resulting from a flank attack (Figure 1b, *vide infra*).

Characterization of the oxidation products of amphiphilic monolayers at the air-water interface is another challenge, especially at the molecular level. Fluorescent methods can provide an overall effect of oxidation to the interfacial structures,[12] but details of the oxidation products can hardly be investigated. The detailed characterization of oxidation products is highly important to study the reaction kinetics and mechanisms. Here we adopt our unique home-developed field-induced droplet ionization mass spectrometry (FIDI-MS) methodology, which is capable of selective "online" *in-situ* sampling of molecules that reside at the air-water interface right after the reactions without any sample handling or transfer, and suffers minimal influence from the bulk of the solution.[13] The FIDI-MS setup is presented in Figure S1. Mass spectrometry has a notable history of studying host-guest chemistry,[6c] and it can provide detailed, fingerprint information of the reaction products. Collectively, FIDI-MS has proven to be an excellent means to examine oxidation chemistry at the air-water interface.

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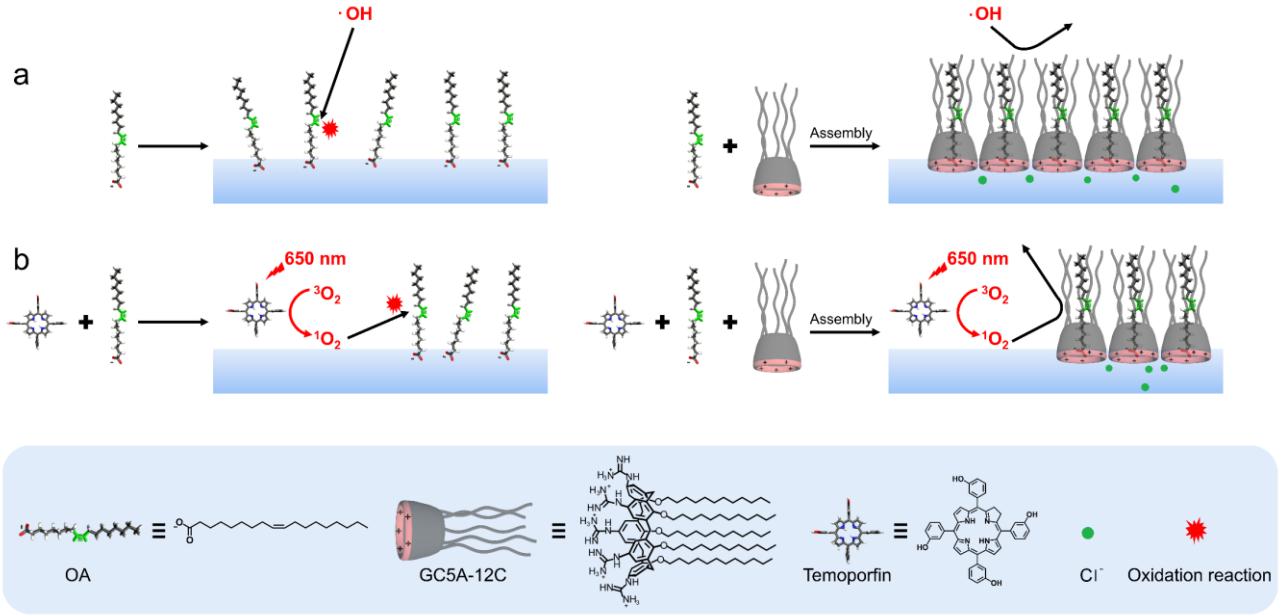

Figure 1. Cartoon showing the host-guest antioxidation mechanisms at the air-water interfaces. (a) Compared to pure OA monolayer, the compact packing of G·OA complex lowers the permeability of OH radicals from the air into the membrane, resulting in a non-sacrificial antioxidation effect. (b) The fact that OA is inside the cavity of G makes G a "cloak" of OA, protecting it from the oxidation by SDO generated in the membrane (flank attack).

Detailed experimental methods are provided in the SI. The binding affinity of G to OA was determined by the indicator displacement assay.[14] By employing G and fluorescein (Fl) as the reporter pair (association constant K_a is $5.3 \pm 0.9 \times 10^6$ M^{-1}),[15] the binding affinity between G nanoparticle and OA was well fitted by a 1:1 competitive binding model, giving a K_a value of $(6.1 \pm 0.8) \times 10^6$ M^{-1} (Figure 2). Such a strong binding is desirable to ensure efficient binding of the host-guest complex at low concentration.

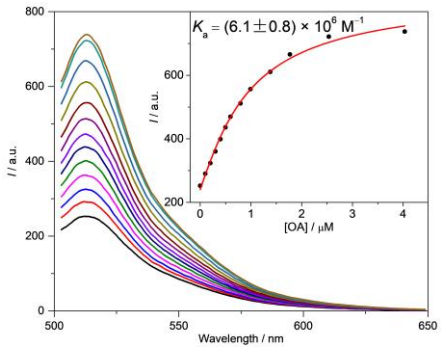

Figure 2. Competitive fluorescence titration of G·Fl (1.0/0.5 μM) with OA (up to 4.03 μM) at an excitation wavelength of 500 nm. The associated titration curve at the emission wavelength of 513 nm and fit according to a 1:1 competitive binding model (inset).

Figure 3a-c presents the FIDI-MS spectra of the OH oxidation of pure OA or OA/G mixture monolayers at the air-water interface. Detailed time-resolved and mechanistic studies of OA oxidation by OH has been reported elsewhere.[13b] Briefly, the unsaturated C=C double bond and saturated C-H bonds of the parent OA^- (m/z 281) are oxidized consecutively by adding carbonyl and hydroxyl functionalities. As shown in Figure 3a, after 90 s exposure to OH, prominent product peaks show up at higher m/z than the parent anion. A small amount of products can be observed at lower m/z, corresponding to C=C bond cleavage products. Around 94% of interfacial OA are oxidized by adding at least one oxygen functionality. Figure 3b shows the anion mode result of OA/G·5HCl mixture at 1:1 ratio, and after a much longer oxidation time (180 s), only a surprisingly low percentage, 6%, of OA are oxidized (m/z 297 and 313). HCl and HNO_3 in the proton bound dimer anions OA^-+HCl (m/z 317, 319) and OA^-+HNO_3 (m/z 344) come from G·5HCl and contamination from air,[16] respectively. Figure 3c displays the result from the same experiment as Figure 3b, but in the cation mode. Triply charged G·OA complexes with different numbers of HCl molecules attached are observed. G and OA clearly show 1:1 binding, and no other ratio was observed, indicating a strong pairwise host-guest interaction. In addition, no obvious oxidation products are observed in cation mode, even though the long pentadodecyl chains of G should in principle be vulnerable to OH oxidation.[17] Apparently the host-guest interaction between G and OA exhibits an excellent antioxidation ability. In our previous endeavors of studying the effect of packing density on the oxidation chemistry at the air-water interface, many examples revealed that the permeability of an oxidizer into the monolayer is significantly lowered as a result of dense packing.[13a, c] Therefore, we postulate that the tight binding between OA and G, and the ionic attraction between protonated G molecules via Cl^- bridges and hydrogen bonds with water make a compactly packed monolayer, which consequently lowers the permeability of OH, quenching the oxidation reactions. Density functional theory calculations reveal that the heights (lengths) of OA and G are about the same when OA is inside G (Figure S3), making the top of the monolayer a flat surface that inhibits accommodation of OH into the interfacial layer.

The scenario described here is presented in Figure 1a. However, Figure 1a takes it for granted that OA is inside the cavity of G. In reality it might not be so, because arene units of G are only connected by single -CH_2- bridges, making its structure very flexible.[18] Since both OA and G are very long molecules, intuitively, it is difficult to imagine favorable kinetics for "sleeving" OA into the channel of G to achieve steric shideling. The question raised here is illustrated by Figure 3d: is OA really sleeved into the long cavity of G, or are they just binding together in a side-by-side

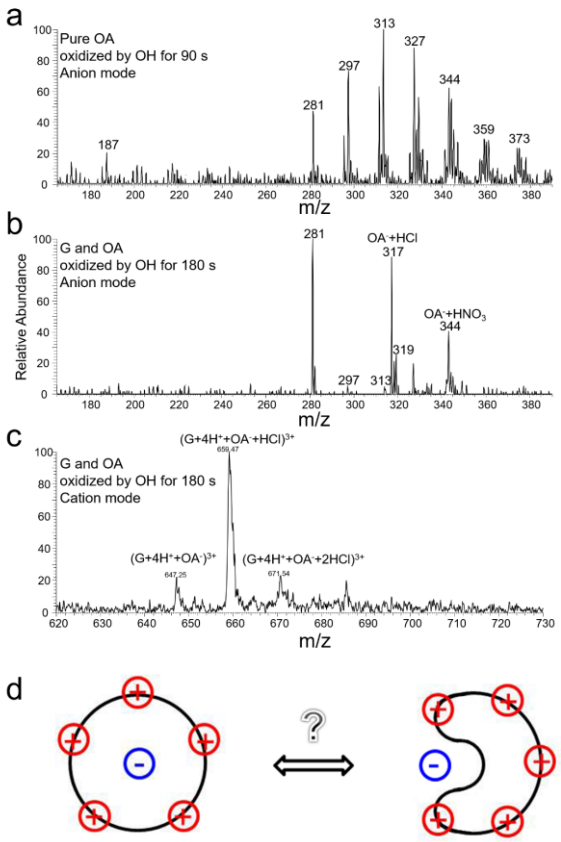

Figure 3. Mass spectrometric results of the oxidation of pure OA and G/OA mixture solution by OH. (a) Anion mode FIDI-MS spectrum including the reactant and products of the pure OA monolayer after 90 s OH exposure. Deprotonated OA^- and its oxidation products appear at 281 and higher m/z. (b) Anion mode FIDI-MS spectrum of the G/OA mixture solution after 180 s OH exposure. Very little oxidation product of OA^- was observed. (c) Cation mode FIDI-MS spectrum of the G/OA mixture solution after 180 s OH exposure. Several peaks belonging to the G·OA complex were observed with no obvious oxidation product. (d) A cartoon raising the question that whether or not OA is inside the cavity of G.

manner? 1D and 2D ^{1}HNMR spectroscopic methods[19] in principle are able to solve the binding situation, but due to the very low solubility of the G·OA complex, NMR fails to provide an answer raised here, and further investigations are needed.

To solve the enigma raised above, and to further test the antioxidation capability of the G·OA complex, the oxidation chemistry initiated by another potent oxidizer, SDO, is presented in Figure 4. SDO is generated by a photosensitizer, T, by shining 650 nm laser to the hanging droplet. Since T is lipophilic,[20] it prefers to stay in the oil phase, i.e. the lipid monolayer as shown by Figure 1b. Therefore, SDO is generated in close proximity to its oxidation targets, i.e. the C=C double bond of OA and the benzene moieties of G. In contrast to the scenario of OH, which is generated in the gas phase and attacks the monolayer from the top, SDO oxidizes molecules in a manner of flank attack (Figure 1b). Ideally, if OA is indeed sleeved into the cavity of G, G should be able to protect OA since the latter is shielded from SDO by the former.

Figure 4a presents a time-resolved study of SDO oxidation of a pure OA monolayer with red light exposure time ranging from 0 to 60 s. Two major products, $OAOOH^-$ (m/z 313) and $OAOH^-$ (m/z 297), are observed with increasing intensity. According to the well-known mechanism of SDO reaction with olefins,[21] the unsaturated chain of OA should be converted to allyl hydroperoxide functionality (-OOH), which can further decompose to a hydroxyl group (-OH) (mechanism provided in Figure S4). Due to the low packing intensity of the OA monolayer,[13c] SDO enjoys a less crowded environment so that it can diffuse more freely to engage oxidation chemistry. Therefore, around 37% of OA is oxidized into $OAOOH^-$ or $OAOH^-$ after 60 s of oxidation time. To further confirm that the oxygen functionality of $OAOOH^-$ and $OAOH^-$ are indeed hydroperoxyl and hydroxyl groups, H/D exchange experiments were performed by using a droplet comprising D_2O. Both -OOH and -OH have one exchangeable H atom.[22] Figure 5 shows that both $OAOOH^-$ and $OAOH^-$ have 1 Da shift, meaning that there is an acidic H in each case. Apparently H atoms are more extensively exchanged by D in $OAOOH^-$ than in $OAOH^-$, consistent with the fact that -OOH is more acidic than -OH.

We next consider the generation of SDO in the mixed G/OA surfactant layer. After 480 s, eight times the oxidation time in Figure 4a, OA^- effectively remains intact, and only 3% is oxidized into $OAOOH^-$ (Figure 4b), indicating a phenomenal antioxidation

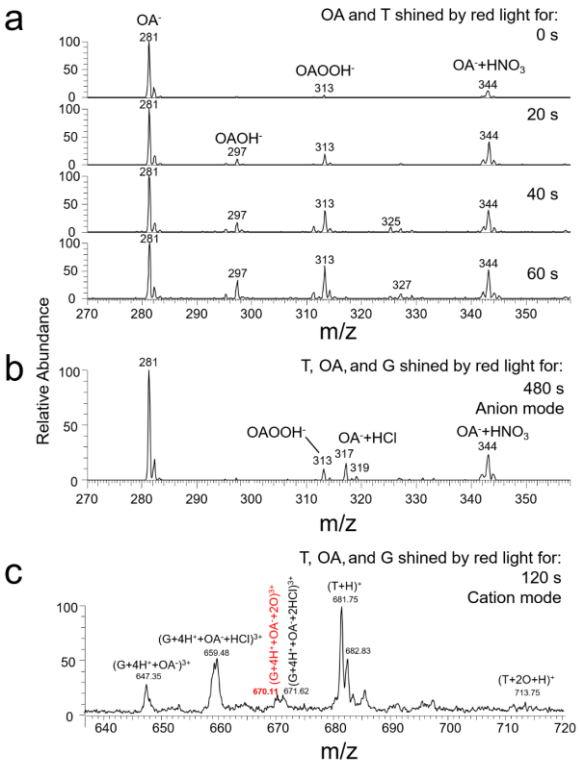

Figure 4. Mass spectrometric results of the oxidation of pure OA and G/OA mixture solution by SDO generated by T. (a) Time-resolved anion mode FIDI-MS spectra including the reactant and products from the pure OA monolayer after 0-60 s red light exposure. Deprotonated OA^- and its major oxidation products $OAOH^-$ and $OAOOH^-$ appear at 281, 297, and 313 m/z. (b) Anion mode FIDI-MS spectrum of the G/OA mixture solution after 480 s red light exposure. Very little oxidation product of OA^- was observed. (c) Cation mode FIDI-MS spectrum of the G/OA mixture solution after 120 s red light exposure. Several peaks belonging to the G·OA complex and one peak belonging to the oxidation product of G were observed.

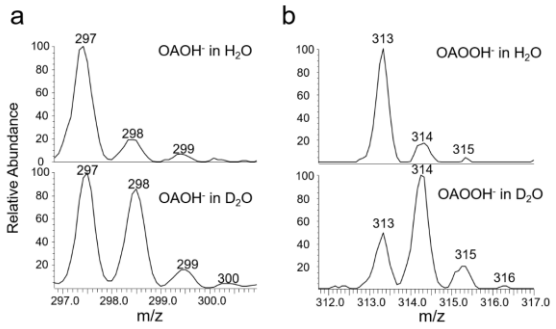

Figure 5. H/D exchange experiment results. (a) FIDI-MS spectra of $OAOH^-$ using H_2O and D_2O as solvents, respectively. (b) FIDI-MS spectra of $OAOOH^-$ using H_2O and D_2O as solvents, respectively.

effect. Since G is shielding OA from SDO, it should be oxidized because each G has five benzene moieties that are vulnerable to SDO oxidation.[21] Figure 4c presents the cation mode result. A new peak at m/z 670.7 shows up (highlighted in red), corresponding to the G·OA complex being oxidized by adding two oxygen atoms through a [4+2] Diels-Alder reaction (Figure S4).[21] However, the extent of oxidation of G (17%) is much lower than pure OA. This might be a result of the difficult conformation change involved in arene oxidation by SDO under this tightly packed environment. It might also be due to the frequent collisions between SDO and the compactly packed environment that induce nonradiative relaxation of SDO.[23] Regardless, we can confidently conclude that in the G·OA host-guest complex, OA is indeed inside the cavity of G and not bound in a side-by-side manner. Figure 4c also displays the signal originated from T. The protonated $(T+H)^+$ shows a strong peak at m/z 681.7, and its oxidation product $(T+2O+H)^+$ only has very low signal, making T a robust PS against photobleaching. A recent study showed that an Ar^+ cation forms a stable radial bond with $B_{12}(CN)_{11}^{2-}$ in the $[B_{12}(CN)_{11}Ar]^-$ anion, suggesting that the side-by-side manner might be indeed present in host-guest complexation even though it is not the case in the current study.[24]

In conclusion, the OH and SDO oxidation chemistries of the monolayers formed by pure OA and G·OA complex at the air-water interface have been studied using the FIDI-MS methodology. When OA is "sleeved" into the long cavity of G to form the G·OA complex, the dense packing of the monolayer greatly decreases the permeability of OH from the gas phase into the monolayer, drastically inhibiting the oxidation of OA and G. Being generated in the monolayer, SDO initiates the oxidation in a different manner involving flank attack. When engaging oxidation from the side, SDO is kept out of the "barrel" formed by G. As a result, only G is oxidized and OA remains intact. Hence, the G·OA complex effectively prevents the oxidation of the antioxidant, OA, initiated by two potent oxidizers (OH and SDO) from different angles (top and side) due to the physical arrangements rather than their chemical reactivity. As a proof-of-principle study, we have demonstrated that host-guest complexation is a promising means for antioxidation. We anticipate that many other molecules, such as bioactive drugs, can be encapsulated by calix[*n*]arenes through complementary binding to achieve, in a well-controlled manner, their antioxidation in membranes that are under oxidative stress.

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Keywords: Mass spectrometry • Supramolecular chemistry • Host-guest complex • Calixarene • Air-water interface

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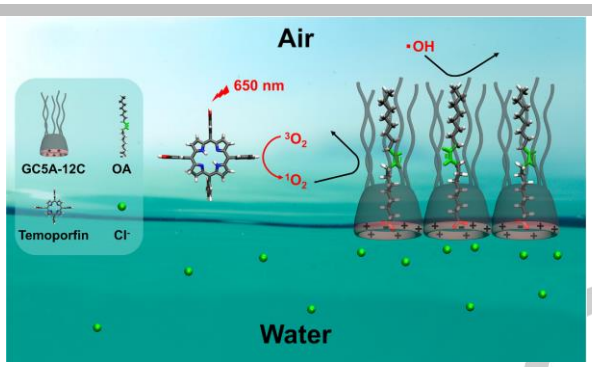
The compact host-guest complexation of calixarene and oleic acid molecules prevents the oxidation of the complex monolayers at the air-water interface from hydroxyl radicals and singlet oxygen.



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Page No. – Page No.
Host-Guest Complexation of Amphiphilic Molecules at the Air-Water Interface Prevents Oxidation by Hydroxyl Radicals and Singlet Oxygen