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The Chemistry of Cardiolipin in the Light of its Role in Mitochondrial Apoptosis

Atef Sobhy Iskander

Cardiolipin is a glycerol-based phospholipid that exists in the inner mitochondrial membrane. Its biological function in this bioenergetics membrane is crucial in all tissues. Cardiolipin interacts with a large number of integral membrane proteins to control their functions. It is closely associated with cytochrome *c* release from the mitochondria, a process that has been identified as the pathway to apoptosis. Such release of cytochrome *c* into the cytosol is accompanied by cellular redox change as a result of oxidative stress. To understand the biological actions of cardiolipin, this article is aimed to shed light on the chemistry of cardiolipin in terms of phospholipid oxidation.

Keywords: Cardiolipin, Cytochrome *c*, Mitochondrion, Phospholipid oxidation, Free radicals.

1. Introduction

Ever since the isolation of cardiolipin (CL) from bovine heart, as marked by Mary Pangborn's pioneer work in 1942[1], progress has been made in understanding the structure, localization, and biosynthetic pathway of this phospholipid. Currently, a consensus is being developed and accepted by researchers in the field that CL is actively participate in the process of programmed cell death (apoptosis). CL is mostly found in the mitochondrial inner membrane, and plays a crucial role for oxidative phosphorylation, generation of electrochemical potential for substrate transport, and participation in the mitochondrial apoptotic pathway. In fact, its name "cardiolipin" derived from its first isolation from bovine heart, but it can be found almost exclusively in mitochondria of all mammalian tissues. To understand the pivotal roles of this unique phospholipid in the mitochondria-dependent steps of apoptosis, this article focuses on the chemistry of cardolipin in terms of phospholipid oxidation.

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2. Structure of cardiolipin

CL is a diphosphatidylglycerol (1,3-*bis*(*sn*-3'-phosphatidyl)-*sn*-glycerol), which its structure was elucidated in 1964 (Figure 1).[2] It is a dimer of phosphatidylglycerol (PG) and phosphatidic acid (PA), whose dimeric structure distinguishes it from other glycerophospholipids. It has four identical acyl residues, two phosphate groups, and three glycerols.

Under physiological pH, one of the phosphate groups is deprotonated making CL a negatively-charged phospholipid. The characteristic acyl chain pattern of CL contains 18 carbons[3], which belongs to linoleic acid ($C_{18:2}$). CL has two chiral centers, one in a pro-*R* and the other in a pro-*S* position with respect to the central carbon atom of the glycerol bridge. Although, natural CL has the *R/R* configuration.

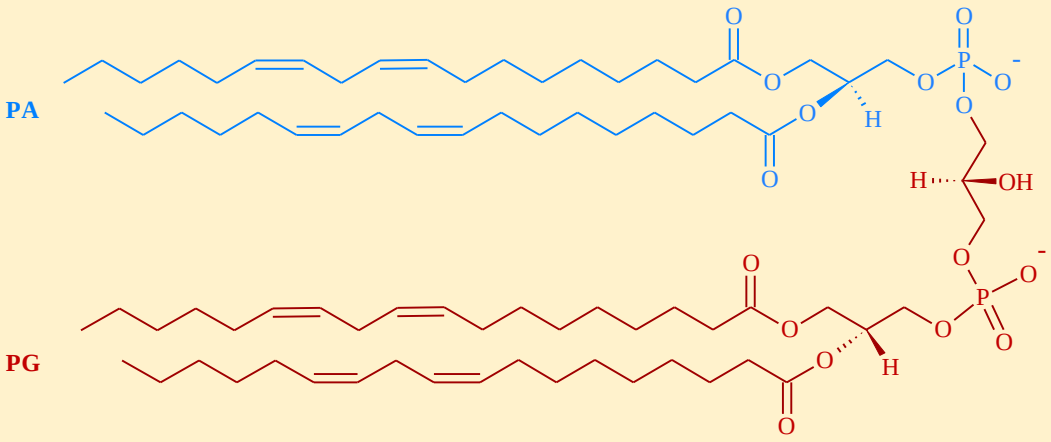

Figure 1. Structure of cardiolipin.

3. The role of cardiolipin in the process of apoptosis

CL exists exclusively in the inner mitochondrial membrane, which constitutes about 25% of the total phospholipids.[4] However, it has been found in the mitochondrial outer membrane (about 4%) at the contact sites linking the outer membrane with the inner one[5], as a result of the fact that CL has the ability to adopt a non-bilayer hexagonal phase (H_{II}).[6] Such unique structure can lead to the fusion of two membranes.[7]

As the existence of CL in the bioenergetic membranes, its biological function in this organelle is clearly crucial in all tissues. It interacts with a large number of integral membrane proteins to control their functions in a way that is shaped by physical and structural properties. In fact, it interacts with the electron transport chain enzymes involved in oxidative phosphorylation, which integrated in the inner mitochondrial membrane.[8,9] These enzymes include complex I (NADH: ubiquinone oxidoreductase), complex III (ubiquin-

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one:cytochrome *c* oxidoreductase), complex IV (cytochrome *c* oxidase), and complex V (ATP synthase). In addition, CL has been found in the quaternary structure of complexes III, IV, and V, as well as in the crystals of *E. Coli* succinate dehydrogenase (complex II).

CL is essential for stimulating and sustaining the functions of thermogenic fat, as it bound to uncoupling protein 1, an integral membrane protein found in the mitochondrial inner membrane of brown adipose tissue that is vital for thermogenesis. Furthermore, CL anchors both of mitochondrial creatine kinase and nucleoside diphosphate kinase to the inner mitochondrial membrane. CL has been implicated in the process of mitophagy (mitochondrial degradation). Once it translocated to the outer mitochondrial membrane, it binds to microtubule-associated protein 1 light chain 3, which is part of the autophagy machinery, and acts as a signal for the process.

The key event in many forms of apoptosis is the release of cytochrome *c* (a 12.3 kDa hemeprotein involved in energy production) from mitochondria, that initiate caspase involved in downstream proteolytic processes of cellular digestion. Such release is regulated by the Bcl-2 protein family. Once cytochrome *c* is released and activates apoptosomes in cytosol, death is the certain outcome for the cell. As part of the mitochondrial electron transport chain, cytochrome *c* has a specific function in transport of electrons between complex III and complex IV. In addition, it is a component of the activation system for caspase-3, which considered to be as an independent function of this hemeprotein.[10,11]

The majority of cytochrome *c* is strongly attached to mitochondrial inner membrane through specific interactions with cardiolipin.[12,13] Cytochrome *c* binds membrane through electrostatic interactions with the head groups of anionic phosphate binding sites of CL. While the hydrophobic cavity of cytochrome *c* interacts with the acyl chains of CL via hydrophobic interactions. Conformational changes of CL alter the interaction of it with cytochrome *c* causing a change in the coordination of heme.[14] In fact, the first process in apoptosis is the dissociation of cytochrome from CL, which is triggered by CL peroxidation. Such peroxidation is catalyzed by reactive oxygen species (ROS).[15] Furthermore, it was shown that the bound cytochrome *c* itself catalyzes CL peroxidation, and acts as minimizing its binding with mitochondrial inner membrane and facilitates permeabilization of the outer membrane.[16] The deficiency of CL leads also to release cytochrome *c* from the inner mitochondrial membrane and enhances stimuli-elicited apoptosis.[17]

Such release of cytochrome *c* from mitochondrial is accomplished through the opening of crista junctions (the pores that link to the internal compartments formed by the inner membrane of a mitochondrion) and formation of outer-membrane pores by pro-apoptotic proteins such as tBid which induced oligomerisation of another pro-apoptotic protein such as Bak or Bax.

The apoptosis-promoting role of CL is demonstrated by its interaction with the pro-apoptotic protein tBid. In fact, tBid acts by two sequential mechanisms: (i) BH3-domain-dependent, inducing oligomerisation of pro-apoptotic Bcl-2 proteins Bax and Bak, and leading to mitochondrial outer membrane permeabilization[18,19]; and (ii) BH3-domain-independent interaction of tBid with CL at the inner and outer membrane contact sites[20], leading to structural and functional deterioration through cristae (the internal compartments formed by the inner membrane of a mitochondrion) remodelling[21] and inhibition of oxidative phosphoryla-

tion.[22] As a matter of fact, Bcl-2 has functions unrelated to apoptosis, however, regulation of Bcl-2 via phosphorylation, proteolysis or interaction with other family members could change it from an inhibitor to a mediator of transmembrane protein trafficking.

As a result of cristae remodeling in response to tBid-induced apoptosis, the structural and functional deterioration of such event comprises cristae fusion, inverted curvature of cristae membranes, and enlargement of crista junction openings.[23] The widening of crista junctions causes a redistribution of cytochrome *c* from inside the intracristal space, where the vast majority of the molecules reside, to the intermembrane space, whence, upon the formation of pores they are subsequently released across the outer membrane. Such loss of cytochrome *c* from mitochondria leads to stimulated superoxide production.[24]

It is noteworthy that a deficiency in CL results in alteration in cell respiration and reduction in ATP production, accompanied by a compensatory increase in glycolysis.[25]

4. The chemistry of phospholipid oxidation

It is now clear how the important role of CL is in maintaining mitochondrial integrity. Indeed, CL is crucial for efficient oxidative phosphorylation and for correct function and structure of the mitochondrial inner membrane. It is also obvious that the decline in mitochondrial respiratory functions and during many cell death processes, reactive oxygen species (ROS) are closely linked in a cycle of CL peroxidation. In fact, CL is a target of ROS or reactive nitrogen species (RNS) due to its unsaturated acyl chains and its close proximity to ROS generation sites. Thus, to understand the influence of ROS on CL, the chemistry of phospholipid oxidation must be taken into consideration. The oxidative modifications to phospholipids dependent mainly on the nature of the oxidant species, as this the mechanism of the oxidative reactions is determined. Such oxidants may derive from exogenous (air pollution, industrial chemicals) or endogenous sources (mitochondrial respiratory chain, myeloperoxidase, etc.), such as those arise from oxidative stress. In fact, the oxidative stress is a result of a situation of perturbations in the redox balance of the cell due to the increasing production of ROS such as $O_2^{-\cdot}$ (superoxide radical), ·OH (hydroxyl radical), and NO· (nitric oxide).[26] As most of ROS are free radical species, therefore, it is of importance to have a cursory glance at the mechanistic aspects of free radicals.

4.1. Free-radical mechanistic considerations

In general, the radical reaction is initiated by a homolytic bond cleavage. It is a chain reaction that consists of three stages: initiation (radical formation), propagation (successive steps generating new radicals), and termination (return to stable molecular species through recombine by coupling or disproportionate, *i.e.*, radical destruction). Radicals can exist in extremely low concentrations, and as long as they exist, they can be generated continuously. The most important processes that remove radicals are (i) combination of radicals with each other (Eq. 1), either by direct bond formation (recombination) or by

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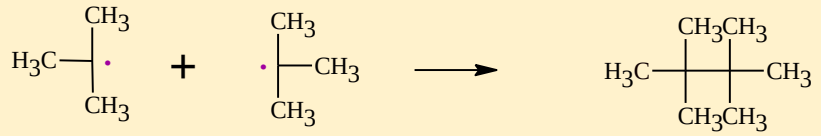
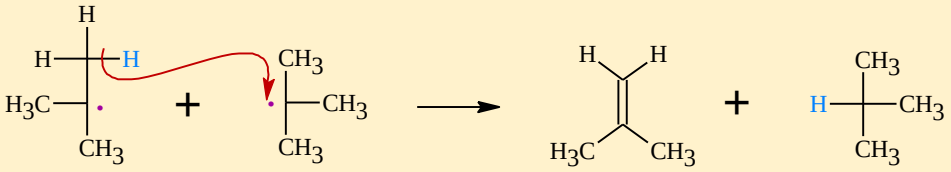
hydrogen atom transfer from one to other (disproportionation) (Eq. 2), and (ii) electron transfer between a radical and an oxidizing or a reducing agent.

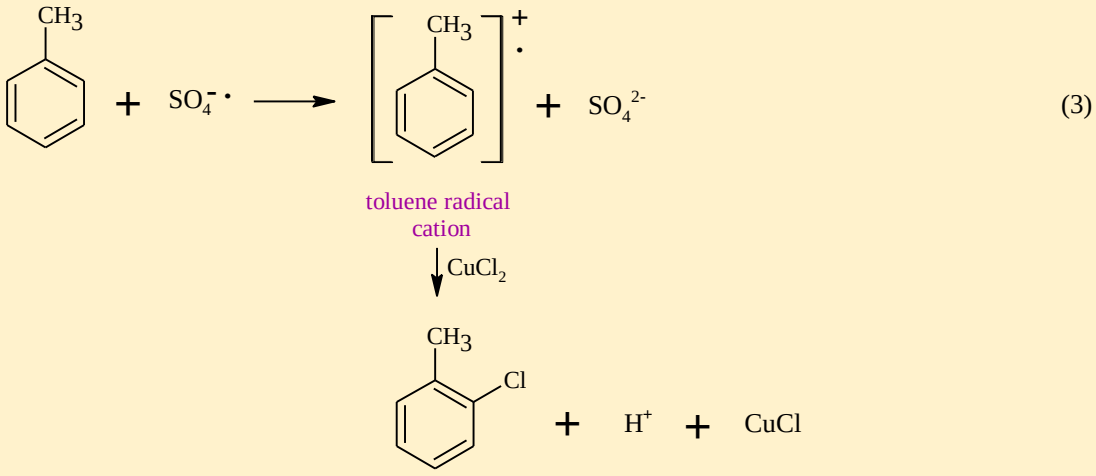


(1)



(2)

In the case of electron transfer to or from a substrate in the presence of a reducing or an oxidizing agent, or an electrode, the reaction proceeds through $S_{RN}1$ mechanism, in which a chain propagates by transfer of a single electron from one radical ion to another.[27] The cause of some substrates to react by a radical mechanism instead of nucleophilic substitution is related to the ability of these substrates to accept an electron faster than it can dissociate into an ion pair or attack by a nucleophile. In addition, this radical mechanism depends on other factors such as the electron donor strength of the nucleophile and on the acceptor ability of the substrate, as well as steric hindrance. For example, a powerful oxidizing agent like $SO_4^{-\cdot}$ removes an electron from an aromatic molecule producing an aromatic radical cation (Eq. 3).[28]



(3)

There are some factors affected the termination stage such as cage effects, steric hindrance, and scavengers, which must be taken into consideration, and will be further illustrated.

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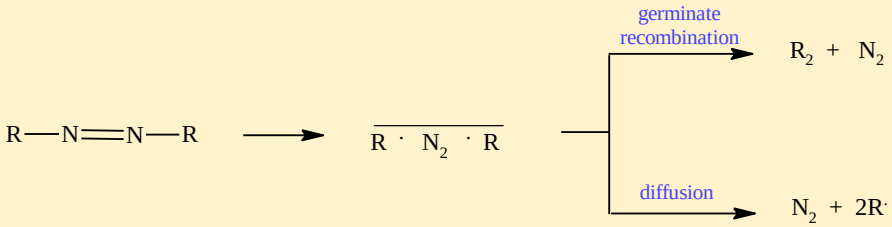
Cage effects

The cage effects play an important role in recombination of radicals. Radicals that are formed in solution by bond homolysis, will be held together briefly in a cage of solvent molecules. In order to resist their destruction, they can compete with diffusion of the radicals through the layer of solvent molecules that surround them in an attempt to escape out of the cage. As a consequence, some of the radicals formed undergo recombination (geminate recombination) (Eq. 4)[29], because such radical recombination is so fast, whereas the escaped radicals undergo further radical generation. In fact, such phenomenon "cage effect" depends on solvent viscosity. The more viscous the solvent, the more difficult it will be for radicals to escape the cage, and the greater the chance that they will recombine with each other.



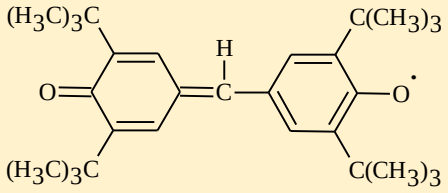
(4)

Persistent radicals

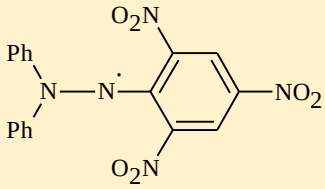
Steric hindrance influences greatly the course of radical reaction. Radicals that have bulky groups near the radical center such as *t*-butyl or trimethylsilyl groups, have lifetimes greater than do the simple alkyl radicals. Consequently, persistent radicals (transient radicals) terminate rather slowly compared to simple alkyl radicals.

Scavengers

Addition of scavengers enhance the termination step, as they react at high rates with radicals. Their role is to pick up all the radicals that escape from the cage. Some typical scavengers are persistent free radicals such as galvinoxyl (**1**) and diphenylpicryl hydrazyl **(2)**. These radicals will not undergo self-recombination, but react very rapidly with transient radicals.



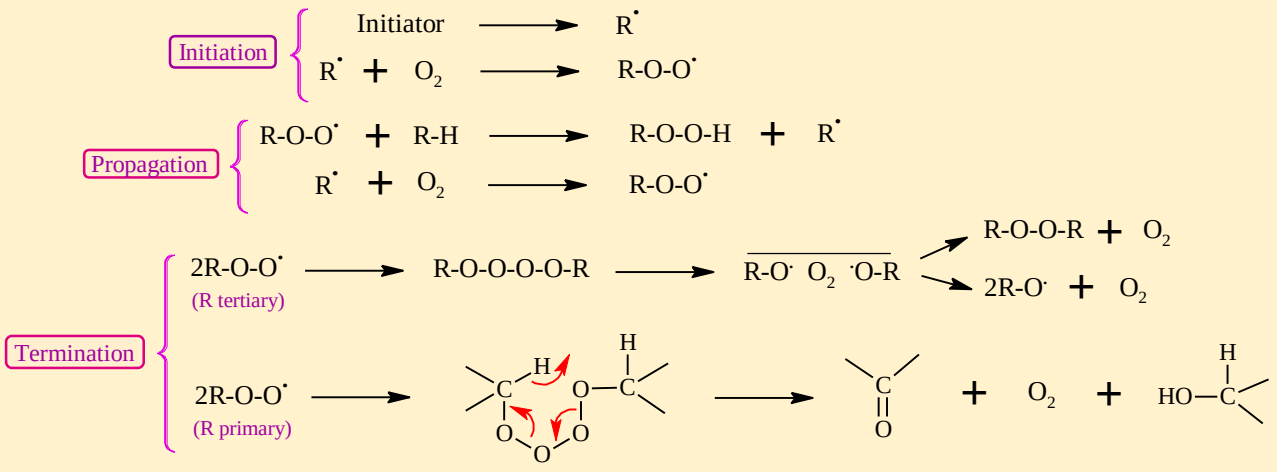
1



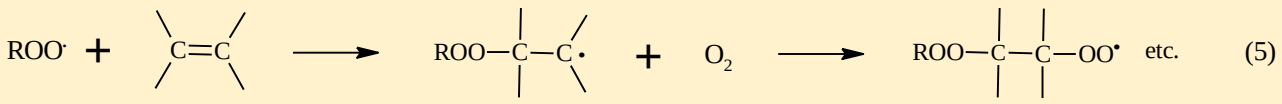
2

4.2 Autoxidation

In an unsaturated system, the radicals initiate the reaction by their addition to the double bond through radical substitutions mechanism S_H2. Radical substitution is a reaction that a radical attacks directly an atom of another molecule displacing from the site of attack another group. For instance, autoxidation, oxidation by molecular oxygen, is a unique process, due to the special nature of O_2, which has two unpaired electrons in the ground state, and so is a triplet state molecule. Such unique feature makes oxygen an efficient trap for radicals (Scheme 1). The oxidation of an unsaturated system is initiated by addition of radicals, and the reaction proceeds *via* radical substitutions mechanism S_H2. Subsequent steps are accompanied by an addition process involving propagation steps (Eq. 5). The termination step of the oxidation of alkene depends on the nature of alkyl radicals. If alkyl radical was primary, the combination of the peroxy radicals to an unstable tetroxide, ROOOOR, takes place rapidly at ambient temperature, by its decomposition by the cyclic Russell mechanism producing nonradical products and terminates the chain. If the alkyl radical was tertiary, *i.e.*, no α hydrogens are available, decomposition takes place by the simple dissociation into oxygen and two alkoxy radicals. As these fragments are produced in a solvent cage, they may combine in the cage, producing peroxide ROOR and terminating the chain. Some of the alkoxy radicals may escape the cage and initiate the chain of events. Further complication can be introduced when a hydrogen transfers from the β carbon of the alkyl radical to oxygen. In this process, the reaction is not terminated, due to the fact that oxygen is behaving like a diradical, but instead produces HOO·, which can resume the chain, and be susceptible for further attack by a radical proceeding an addition-oxidation process (Eq. 5)



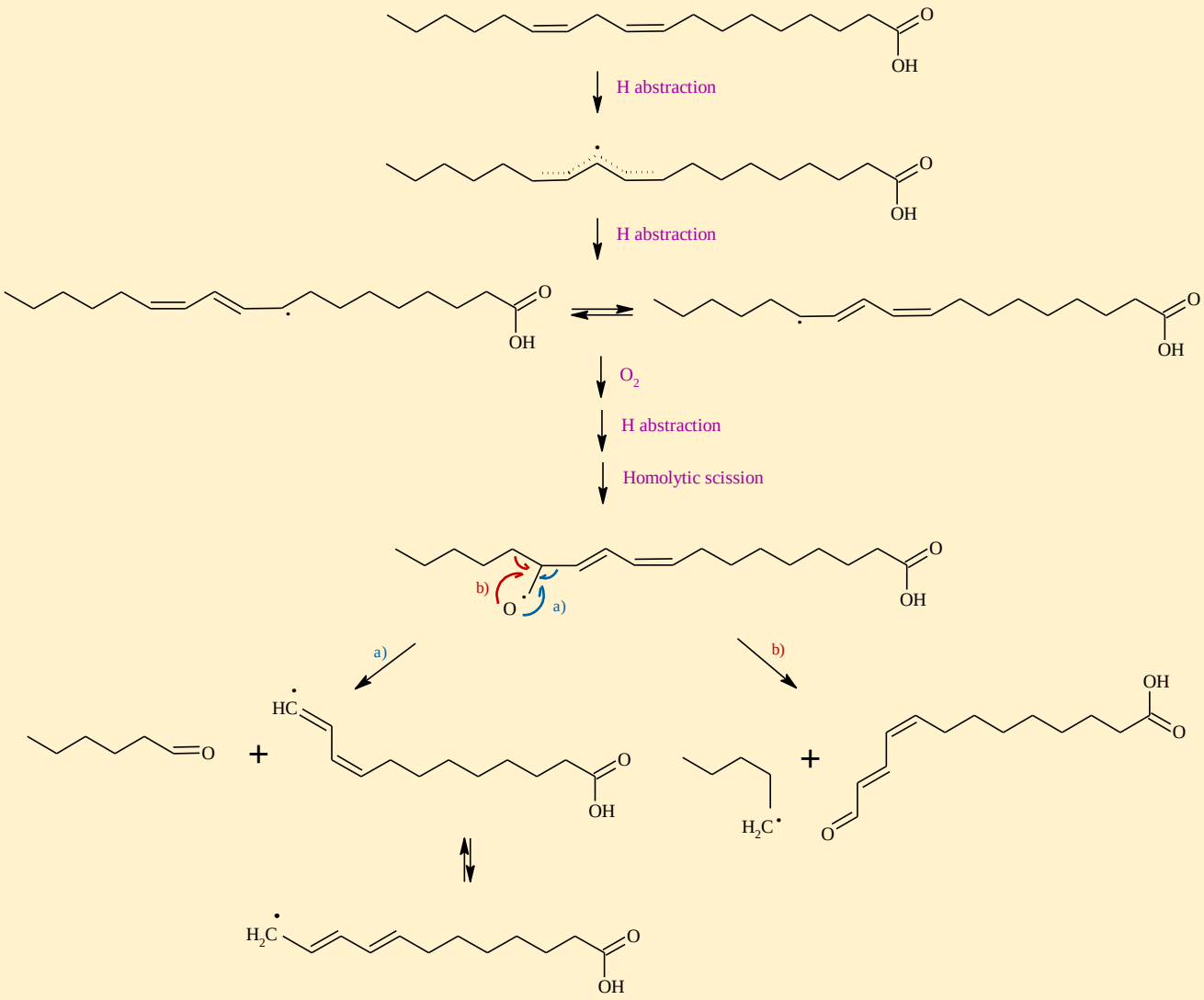
Scheme 1. The mechanism of autoxidation reaction.



In order to prevent autoxidation reaction, inhibition can be achieved by: (i) the addition of substances that will break the kinetic chains, such as the hindered phenols which have in the –OH group a readily abstracted hydrogen that can produce unreactive radical and hence not participated in the propagation of the chain; or (ii) substances that prevent their initiation, such as substances that destroy peroxide initiators, e.g., compounds containing unoxidized sulfur.

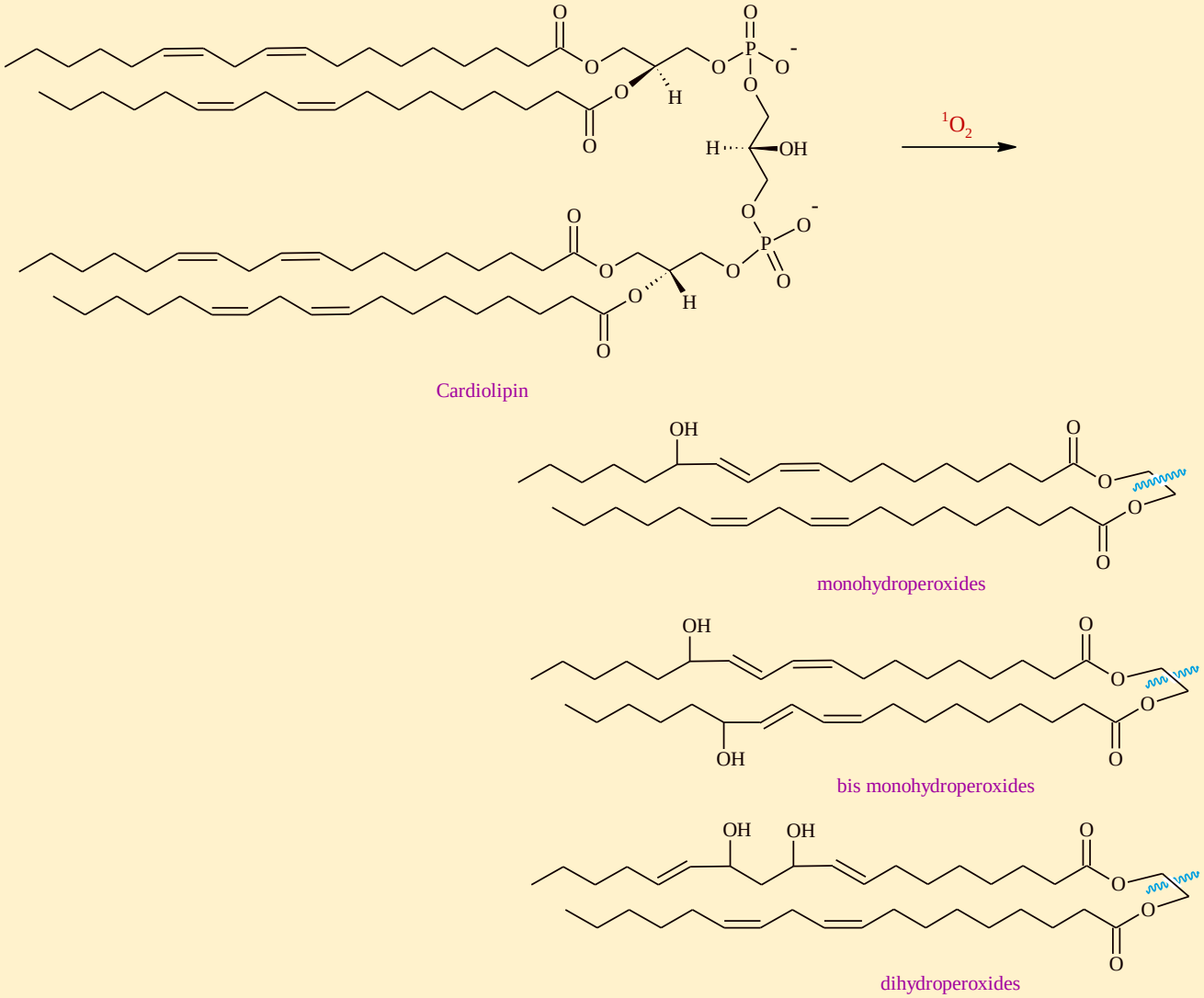
5. The chemistry of phospholipids oxidation

In general, oxidation of glycerophospholipids that linked to the *sn-1* and *sn-2* positions results in a wide variety of different reaction products, depending on chain length and degree of unsaturation. In mammalians, the *sn-2* position of diacylglycerophospholipids is linked to polyunsaturated fatty acids, that are susceptible to oxidative modification. As a result of the low dissociation energy of their bis-allylic carbon-hydrogen bonds, a hydrogen atom can easily be abstracted by a molecular oxygen, leading to the formation of a highly reactive phospholipid radical species with the radical centred on the allylic carbon atom (the initiation stage of lipid peroxidation) (Scheme 2).[30] Subsequently, the reaction may follow rearrangement of a peroxyl radical (ROO·) to a new carbon-centred radical. Furthermore, the presence of other bis-allyl hydrogen atoms in polyunsaturated fatty acyl chains may lead to the addition of O_2 several times on each of acyl residue. In this propagation stage, these intermediate peroxidation products lead to a situation of continuing the radical diffusion, as they can stabilize themselves by abstracting hydrogen atoms from neighboring molecules leading to the formation of new carbon-centred radicals on adjacent fatty acyl chains. Termination of such event can be achieved either by the intervene-tion of lipophilic chain-breaking antioxidants, or under conditions of high levels of initiating radical concentration which may support radical-radical interactions leading to the formation of stable phospholipid products.

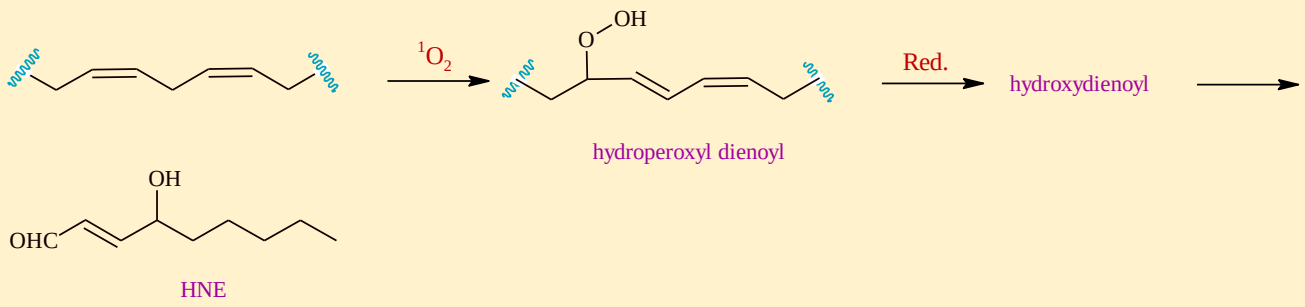


Scheme 2. Possible routes for homolytic β-scission of alkoxyl radical. Products formed via route (a) are hexanal and alkenyl radicals, while products formed via route (b) are pentyl radicals and 9,11-tridecedienoic acid.

It was demonstrated that oxidation of CL generated significant amounts of monohydroperoxides and bis monohydroperoxides as major products (Scheme 3).[31] Subsequent reduction produced potent lipid electrophiles including the high toxic 4-hydroxy-nonenal (4-HNE) *via* a mechan-ism involving cross-chain peroxyl addition followed by decomposition (Scheme 4).[32] 4-HNE is a high reactive aldehydic metabolite, which results in multiple effects on different protein, changing their function and stability.[33]



Scheme 3. $^1O_2$-mediated oxidation generated all three types of structures, whereas the radical oxidation generated only mono-hydroperoxides and bis monohydroperoxides as major products.



Scheme 4. Formation of 4-hydroxynonenal (HNE).

6. Conclusion

Accumulating evidence points to the complex interplay of three events necessary for the release of apoptogenic factors: i) the opening of crista junctions; ii) the dissolution of cardiolipin-cytochrome *c* association; and iii) the formation of mitochondrial outer membrane pores. It is also becoming clear that peroxidation of the acyl chains of cardiolipin constitutes an important factor in apoptosis process.

There are two main issues related to the release of cytochrome *c* from mitochondria, increase the challenge of studying the mitochondrial integrity; neutralizing of the redox potential within the mitochondria; and maintaining the cellular concentration of cardiolipin, would be an appealing target for drug development.

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Snapshots of some topics of interest of recent notable advances in chemistry

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Managing Director / Founder

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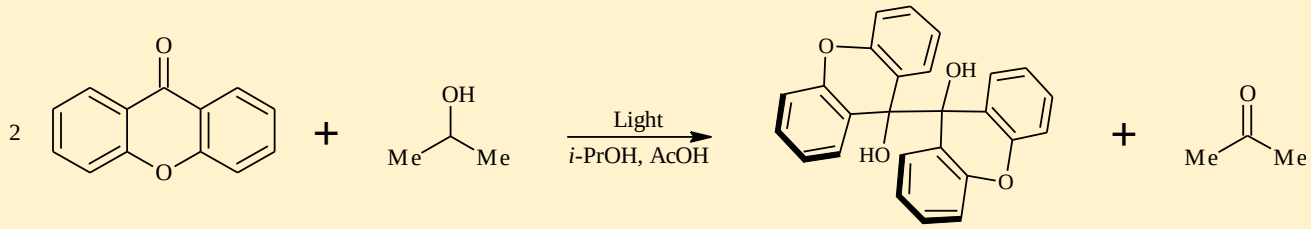
Strained Vicinal Diol as a Reductant for Coupling of Organyl Halides

A sterically strained vicinal diol is employed as reductant for nickel-mediated homo- and cross-coupling reactions of organyl halides.

Toward an efficient reductant for coupling of organyl halides, Ishida and co-workers reported a recycled sterically strained vicinal diol compound for nickel-catalyzed homo- and cross-coupling reactions of organyl halides.

The diol **2** is prepared by an endergonic reductive dimerization reaction of xanthone **1**, which is driven by irradiation of light such as natural solar light (Scheme 1). The diol is stable under air at room temperature for months.



Scheme 1. Photoinduced reductive dimerization of xanthone.

Photoinduced dimerization reaction is considered as a step to harvest light energy which is stored in the diol **2** in a form of steric strain. The stored energy is released when **2** is treated with an alkoxide or hydroxide base in the presence of $Ni(II)(acac)_2$ and COD. The nickel center is ultimately reduced to yield $Ni(0)(cod)_2$ along with regeneration of two molecules of xanthone **1**. The recycled **1** can be subsequently used for another round of the light-driven dimerization reaction.

The diol **2** served as a reductant for a homo- coupling reaction of aryl bromide **3** in the dark (Scheme 2), whereas its role in cross-coupling reaction of aryl bromides **3** with alkyl iodides **5** produced 3-octylanisole **6** (Scheme 3).

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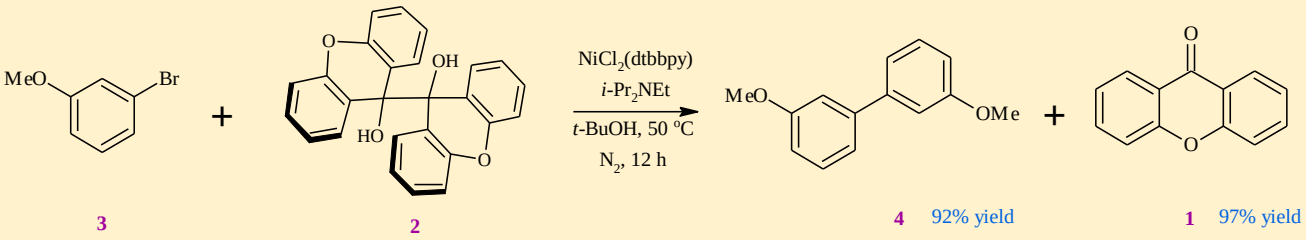
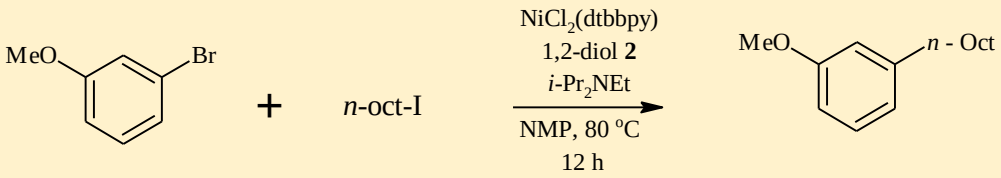


3 2 4 92% yield 1 97% yield

Scheme 2. Diol **2** as the reductant for homo-coupling of **3**. dtbbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine; *i*-Pr_2Net = Hünig's base.



3 5 6 79% yield

Scheme 3. Cross-coupling of **3** with **5**. NMP = *N*-methylpyrrolidone.

The method demonstrates a unique way to use light as the source of energy to drive synthetic transformation.

Review

N. Ishida, Y. Masuda, F. Sun, Y. Kamae, M. Murakami, *Chem. Lett.*, **2019**, *48*, 1042-1045..

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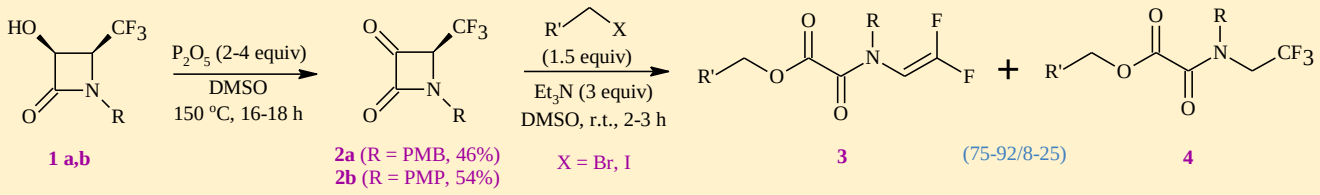
Synthesis of Fluoronated Amido Esters *via* C3-C4 β-Lactam Bond Fission

A synthetic route is described for formation of fluorinated amido esters from 4-trifluoromethyl-3-oxo-β-lactams through C3-C4 bond fission.

This snapshot highlights the reported preparation of a value-added fluorinated building block, which may be of interest in pharmaceutical research. Generally, the interest in fluorinated compounds is related to the unique physical and chemical properties associated with fluorine atom, which has the ability to influence the pharmacodynamics and pharmacokinetic properties of therapeutically active compounds.

The deployment of 4-trifluoromethyl-3-oxo-β-lactams as versatile precursors for the synthesis of a variety of β-lactam and non-β-lactam products was employed in order to pave the way for further construction of an additional side chain through abstraction of the acidic C4-proton in the α-position with respect to the oxo group and the CF_3 moiety.

The precursor 3-oxo-4-(trifluoromethyl)azetidin-2-ones **2** was obtained in a moderate yield from 3-hydroxy-4-trifluoromethyl-β-lactam **1** *via* Albright-Onodera oxidation using P_2O_5 in DMSO (Scheme).



1 a,b — **2a** (R = PMB, 46%), **2b** (R = PMP, 54%) — X = Br, I — **3** — (75-92/8-25) — **4**

Scheme. Synthesis of 4-trifluoromethyl-3-oxo-β-lactams 2 and their transformation into amidoesters 3 and 4.

The preparation of fluoronated amidoesters was accomplished via the treatment of ketones **2** with 1-iodopropane in DMSO at room temperature to give a mixture of propyl 2-[(2,2difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate **3a** as a major product and propyl2-oxo-2-[(4-methoxybenzyl)(2,2,2trifluoroethyl)amino]acetate **4a** as the minor product. The reaction is proceeded *via* an unprecedented C3-C4 β-lactam bond fission.

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Review

H. D. Thi, H. Goossens, D. Hertsen, V. Otte, T. Van Nguyen, V. Van Speybroeck, M. D'hooghe, *Chem. Asian J.*, **2018**, *13*, 421–431.