

Superoxide Anion Radical, A Multipotent Reagent: A Review

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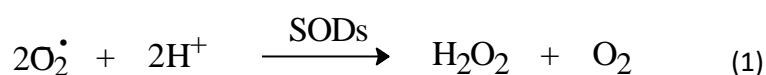
Abstract

Superoxide anion radical (O_2^\bullet), is a reactive oxygen species (ROS) and plays a key role in various life processes. From chemical view point, it is a multipotent reagent.

Keywords: Superoxide ion, generation, chemical reactivity

Introduction

In the past two hundred years, the life supporting molecule oxygen (O_2) has been characterised, scrutinized and applied in many ways. Oxygen in the ground state tends to act like a biradical and most of its oxidation reactions proceed by one electron step involving free radical intermediates [1]. If we see the electron affinity of oxygen some involvement of superoxide anion radical (O_2^\bullet) in biological oxidations might be anticipated. The experimental detection of O_2^\bullet as a product of enzymatic reduction [2-4] of molecular oxygen recognized function of superoxide dismutases (SODs) [2], an enzymatic catalyst for the disproportionation of O_2^\bullet to O_2 and H_2O_2 (eq. 1, 2).



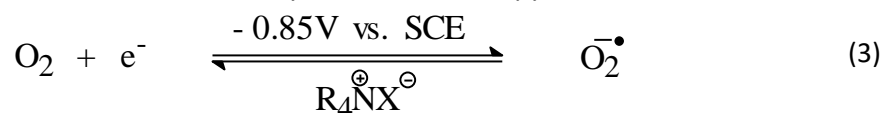
The chemistry and biology of superoxide anion radical (O_2^\bullet) have come to the forefront of interdisciplinary research owing to its biochemical implication and as a species of relatively unexplored chemical reactivity. The ability of superoxide anion radical to exhibit multifarious reactions and its potentially damaging role in various diseases have engendered considerable interest in this unique species. O_2^\bullet has been incriminated to play a crucial role in numerous pathologies such as cancer, heart attack, diabetes, inflammation, acute lung injury, Parkinson's, Alzheimer's disease, renal disease and aging [3-14].

The chemistry and reactivity of O_2^\bullet have been the subject of considerable interest to chemist and biochemist during the past five decades. Also, the discovery that O_2^\bullet is a respiratory intermediate

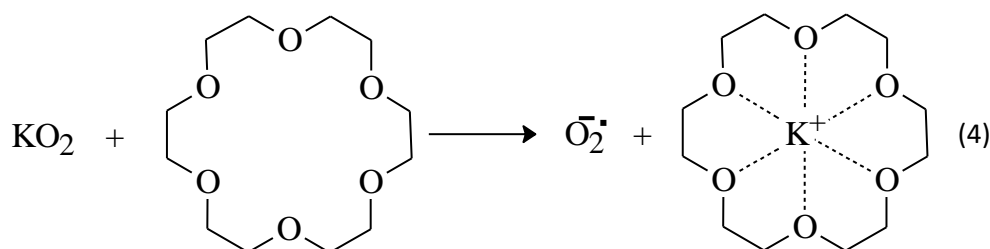
of aerobic organism has prompted widespread and deep interest in the chemical properties and reactivity of O_2^\bullet with organic functional groups.

Generation of Superoxide Ion

At present there are two practical methods are in use for preparing O_2^\bullet in aprotic media. The first method involves one-electron reduction of molecular oxygen at -0.85V vs SCE using tetraalkylammonium salt as supporting electrolyte (eq. 3) [15]. The solvents generally used are DMF, DMSO, acetonitrile, methylene chloride and pyridine.

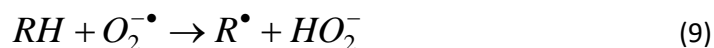
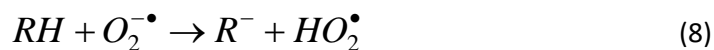
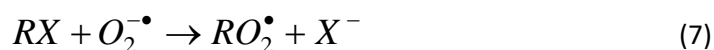


The second method utilises superoxide salts which one commercially available and a source of O_2^\bullet . Potassium superoxide (KO_2) in complexation with 18-crown-6 [16] or tetraethylammonium bromide [17] used for synthesis (eq. 4, 5).



Chemical Reactivity of Superoxide Ion

Superoxide anion radical has a dual character, being a negatively charged species, O_2^\bullet displays basicity and nucleophilicity whereas the unpaired electron accounts for its ability to function as an electron transfer agent and participation in free radical reactions. There are four basic modes of action to O_2^\bullet in aprotic media viz., electron transfer, nucleophilic substitution, deprotonation and H-atom abstraction (eq. 6-9) [18-21].



Reactions of Superoxide Ion with Different Functionalities

Some general trends of $O_2^{\bullet-}$ reaction with different functionalities [3, 21] are briefly outlined below.

Alkyl halide and Sulfonates

Aliphatic halides and Sulfonates, on reaction with $O_2^{\bullet-}$ undergo rapid nucleophilic substitution yielding peroxides, hydroperoxides, alcohols, aldehydes or acids depending on the the reaction conditions and work up employed [15, 17, 22-24].

Acid Chlorides, Anhydrides and Esters

Acid chlorides and anhydrides react rapidly with $O_2^{\bullet-}$ in aprotic solvents producing diacyl peroxides which are further susceptible to reaction with $O_2^{\bullet-}$. The reaction of carboxylic esters with $O_2^{\bullet-}$ is generally quite slow producing carboxylic acids and alcohols [25, 26]. Tetraethylammonium superoxide brings about a cleavage of anhydrides into dicarboxylic acids and lactones to γ -ketocarboxylic acids [27, 28].

Aldehydes and Ketones

Many reports indicate that $O_2^{\bullet-}$ oxidises aldehydes to carboxylic acids [25, 26, 29]. Ketones having acidic proton undergo base-catalysed oxidative processes. [3, 30]

Amides, Thioamides, Nitriles and Imines

Amides are normally inert, although with large excess of $O_2^{\bullet-}$ and prolonged reaction time, some hydrolysis products are observed [26], Nitriles too are normally reluctant to $O_2^{\bullet-}$, although there are some reports of conversion of nitriles to amides [26, 31]. $KO_2/18$ -crown-6/ultrasound accelerates the formation of α -benzoylbenzylcyanide from benzyl cyanide [32]. Thioamides and imines show varying reactivities with $O_2^{\bullet-}$ [33, 34].

Sulfur Compounds

The reaction of $O_2^{\bullet-}$ with a variety of thiols which gives disulphides [35, 36]. Aryl and alkyl disulfides, thiosulfonates, thiosulfonates and sodium thiolates are converted to their corresponding sulphinic and sulfonic acids [37]. Sulfides are oxidised to corresponding sulfoxides by superoxide activated by BF_3 in dry acetonitrile [38]. Tetraethylammonium superoxide brings a deprotection of a variety of 1,3-dithiolanes to carbonyl compounds [39]. $O_2^{\bullet-}$ in ionic liquids has been used for the oxidative desulfurization of benzothiophene and dibenzothiophene [40].

Cation and Cation Radicals

The nucleophilic attack of $O_2^{\bullet-}$ at positively charged centres has been reported by several groups. The reaction of tropylium ion with $O_2^{\bullet-}$ leads to benzaldehyde, benzene, cycloheptanone and carbon monoxide in 2:2:2:1 ratio [41]. Superoxide ion reacts with alkyl imidazolium cations of imidazolium based ionic liquids give 2-imidazolones [42].

Conjugated Ketones

Diketones and keto acids undergo cleavage to give carboxylic acids by $O_2^{\bullet-}$ [43]. The reaction of 2,3-dimethyl-1,4-naphthoquinones and other Vitamin K related compounds give the corresponding oxirane and phthalic acid [44]. Various chalcones were cleaved to carboxylic acid by the reaction with electrochemically generated superoxide ion [45]. Cyclohexenones possessing available acidic α or γ -hydrogens underwent $O_2^{\bullet-}$ mediated base catalysed autoxidation [46].

Olefins

Simple olefins are resistant to $O_2^{\bullet-}$. However electron deficient olefins are susceptible to cleavage by $O_2^{\bullet-}$ [47, 48]. Polyhalides reacted with $O_2^{\bullet-}$ to cause cooxidation of olefins to the corresponding oxides [49].

Aryl System

Unsubstituted aromatic hydrocarbons such as benzene, naphthalene, anthracene etc. are unreactive towards $O_2^{\bullet-}$. However when electron withdrawing groups are present the nucleophilic aromatic substitution is observed [50, 51].

Peroxides

The peroxides on reaction with $O_2^{\bullet-}$ gives carboxylic acids [25, 26]. The reaction of $O_2^{\bullet-}$ with diacylperoxides and anhydrides is observed and giving rise to an epoxidising species [52]. Tetramethylammonium superoxide reaction with other tert-butyl or tert-amyl hydroperoxide in acetonitrile yields corresponding alcohols [53]. The production of singlet oxygen has been quantified in the reaction of superoxide with benzoyl peroxide [54].

Alcohols and phenols

Alcohols, in general, are disproportionated by $O_2^{\bullet-}$ [52]. Superoxide ion reacts with primary and secondary alcohols to form corresponding carbonyl compounds [55-59]. An oxidative cleavage of glycols and related dihydroxyarenes has been accomplished [60]. The reaction of $O_2^{\bullet-}$ with aromatic hydroxylic substrates such as phenols, o- and p-dihydroxyarenes and α -tocopherol & related 6-hydroxychroman compounds results in oxidation products [61]. KO_2 oxidation of cis-4,5-dihydro-4,5-dihydroxypyrene gives lactone [62]. Superoxide induced synthesis of 2-substituted benzoxazole from phenolic Schiff base has been reported [63, 64].

Amines

The reaction of $O_2^{\bullet-}$ with aromatic amines and 1,2-disubstituted hydrazines yields azobenzenes [65]. Monosubstituted alkyl and aryl hydrazines are readily oxidised by $O_2^{\bullet-}$. Dialkylamines are instantaneously oxidised to dialkyl nitroxides [66]. Also aromatic primary amines have been directly converted to nitro compounds [67]. Tetraethylammonium superoxide promoted synthesis of 2-arylbenzimidazoles from Schiff bases has been demonstrated [68]. Hantzsch dihydropyridines produce the corresponding aromatized pyridine derivatives [69-71]. Winterfeldt reaction using KO_2 and 18-

crown-6 ether has been reported [72, 73]. Superoxide ion can be used in the carbamation and dithiocarbamation of amines [74-77].

Saturated Hydrocarbon

The reaction with active C-H linkage occurs via initial proton transfer. Ketones are converted to either α – diketones or acids. Most benzylic and allylic hydrogens are inert to $O_2^{\bullet-}$, although 1,4- and 1,3-cyclohexadienes are converted to benzene [78, 79]. Methyl pyridines and methylpyridine-N-oxide are oxidised by electrogenerated $O_2^{\bullet-}$ to carboxylic acid in low yield [80].

Conclusion

It is evident that the chemistry and reactivity of superoxide ion, $O_2^{\bullet-}$ has paid a much more attention due to its characteristic nature to perform a variety of organic reactions i.e., electron transfer, nucleophilic action, deprotonation, etc. The present review extends the synthetic potential and versatility of this novel reagent in organic synthesis.

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