Novel Synthesis of Keto acid Precursor Derivative for Oxidation of Lambda-Carrageenan Polysaccharide by Alkaline Permanganate

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ABSTRACT

Novel Keto-acid derivatives of lambda-carrageenan (LCAR) as sulfated polysaccharides were synthesized through LCAR oxidation by permanganate ion in alkaline media at pH`s > 12. Stoichiometric molar ratios of LCAR, MnO_4^- and NaF were mixed in alkaline solutions of pH >12. The mixture was stirred until reaction completion (~48 hr), then the formed colloidal precipitate of MnF_4 was isolated by filtrations. A rotary evaporator was used to concentrate the filtrate to about one-fifth of its original volume, and then acidified by acetic acid to pHs of ca. 5-6. Vacuum evaporation was applied to that remains filtrate until drying, and then it was kept in a desiccator for use. The hydroxyl amine and 2,4-dinitrophenyl hydrazine were used to identify the oxidation product. The formation of the corresponding 2,4-dinitrophenyl hydrazone and dioxime derivatives, respectively, indicated the formation of ketoacid-LCAR as the final oxidation product. Such oxidation products can be applied as alternative promising in pharmaceutical, medicine, biomedicine and food industry technologies.

Key Words: *Novel synthesis, Ketoacid LCAR, Pharmaceutics, Biomedicine*

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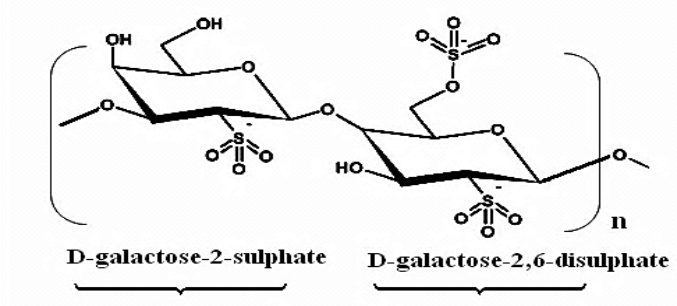
INTRODUCTION

Carrageenan polysaccharides (CAR) are linear sulfated hydrophilic polysaccharides extracted from specific red seaweeds. They consist of disaccharide repeat units of galactose and (3,6) anhydrogalactose links. There are different types of carrageenans named kappa (KCAR), iota (ICAR), and lambda (LCAR) and are commonly linked by glycosidic unions [1, 2]. The configuration structure of LCAR can be illustrated in **Figure 1**.



$(C_{12}H_{17}O_{19}S_3)^{3-}{}_n$

Figure 1. Configuration structure of LCAR.

Lambda-carrageenan as polysaccharide is recognized as an alternative promising future pharmaceutics, medicine, biomedicine, and food industries. This is because the LCAR substrate has wide applications in pharmaceutical formulations such as toothpaste, firefighting foams, air fresher shampoo and cosmetic cream, tissue engineering,

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food industry, and as a carrier in drug delivery, etc [3-5]. This is due to its high bioactivity as an antioxidant, anticoagulant antiviral, antibacterial, antitumor, and immune- modulating properties [4, 6, 7]. It can be attributed to its oblivious physical properties such as biodegradability, bio- compatibility, nontoxicity, hydrophilicity, environment eco-friendly, and low cost.

The presence of carboxylate, hydroxyl, and sulfate functional group moieties within the monomers of the macromolecular chain backbone matrix of polysaccharides particularly the cited L-carrageenan (LCAR), explains its high water solubility and gelling ability

Since all polysaccharides are considered as stronger reducing agents (electron promoters), this fact renders the LCAR substrate the capability to reduce the permanganate ion (VII) as a strong oxidizing agent in either acidic or alkaline medium, giving it the corresponding Mn(II) or Mn(IV) species, respectively, with the simultaneous oxidation of LCAR forming either ketoacid (or ketoaldehyde) as precursor derivatives depending on the experimental conditions such as the nature of the solvent, the nature of the oxidant, and the pH of the media.

Permanganate ion is a strong oxidizing agent of multi-equivalent nature that is utilized to oxidase most organic [8, 9] and inorganic [10-12] substrates. In addition, Hassan *et al*. evaluated the oxidation kinetics of some alcoholic macromolecules of either natural polymers such as polysaccharides [13-15] or synthetic ones as poly (vinyl alcohol) [16] and poly (ethylene glycol) [17] by permanganate ion in alkaline media at pH's > 12. They presented data on the secondary alcoholic groups' oxidation in case of non-sulfated polysaccharides results in corresponding keto-derivatives formation [18-22]. In contrast, the oxidation of primary and secondary alcohols in sulfated polysaccharide gives the corresponding ketoacid derivatives such as chondroitin-4-sulfate [23] and carrageenans [24, 25]. Unfortunately, the literature survey indicated that no information had been reported on the LCAR substrate oxidation by alkaline permanganate ion in alkaline media owing to the kinetics complexity.

Considering the mentioned points and our desire for the synthesis of keto and ketoacid derivatives of polysaccharides as natural polymers using various oxidants, the present work has been undertaken for the synthesis of a novel ketoacid derivative from the lambda carrageenan substrate oxidation by alkaline permanganate, which can be regarded as an alternative promising in future applications in pharmaceutics, medicine, biomedicine and food industrial technology.

MATERIALS AND METHODS

Materials

Lambda-carrageenan (L-CAR) applied in this research was (Fluka reagent) and was utilized without further purification.

Procedure for preparing of LCAR sol

This procedure of preparation was performed as described earlier [24, 25].

An analytical grade existed in all other utilized materials. In all preparations, doubly distilled water was applied.

Synthesis of keto-acid oxidation derivative of sulfated lambda-carrageenan (LCAR)

A 5 g of LCAR powder was dissolved in 350 cm^3 of deionized water with pH adjusted to pH ≥ 12 by NaOH reagent. This procedure takes place by adding the powder to the solution while blending the mixture permanently and quickly to prevent the formation of the lump, which swells with difficulty [24, 25]. A mixture of 150 cm^3 dilution involving 5.43 g of NaF and 5.17 g of MnO_4^- was slowly added by stepwise addition over 2 hours to the LCAR sol reagent. The reaction mixture was blended at room temperature for about 48 h for reaction completion. Then, the formed colloidal sol of MnF_4 was filtered off. A rotary evaporator was applied to the concentration of the filtrate solution to become one-fifth of its original volume. The resultant solution was acidified to a pH of ca.5-6 by dilute acetic acid. The final solution was dried under vacuum and subjected to elemental analysis and IR spectroscopy.

The mechanistic and kinetics of oxidation of LCAR by alkaline permanganate have been described in detail elsewhere [25, 26].

Polymerization test

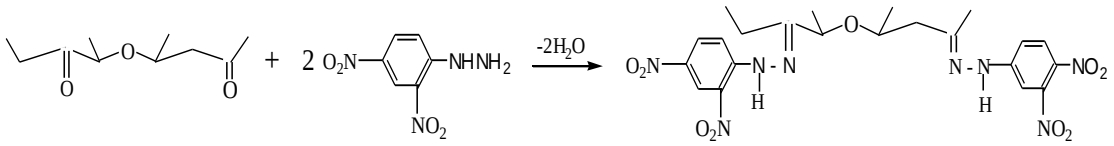
Through adding acrylonitrile to the partially oxidized reaction mixture, the formation of free radicals during the oxidation progression was investigated. The negative test of polymerization showed the nonexistence of free radical intervention in the oxidation process.

Identification of oxidation product

The 2,4-dinitrophenylhydrazine and hydroxylamine were used to identify the oxidation products described elsewhere [20-27].

Using 2,4-dinitrophenylhydrazine

A diketone solution was heated with a solution of 2,4-dinitrophenyl hydrazine on a water- bath and gave a yellow precipitate of the hydrazone derivative of LCAR.

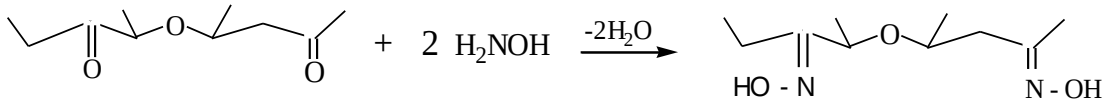


diketone 2,4-dinitrophenyl hydrazone derivative

ANAL: 2,4-dinitrophenyl hydrazone derivative of lambda-carrageenan $C_{24}H_{19}O_{26}N_8S_3$ (931): Calcd. (found): C, 30.93 (30.96); H, 2.05 (2.01); N, 12.03 (12.12). 3320 (NH of hydrazone); IR: 3415 (OH of COOH group); 1262 cm^{-1} (C—O—C of LCAR); and 1660 (C=N of hydrazone).

Hydroxylamine usage

After being heated by hydroxylamine on a water bath, the diketone solution gave white precipitate. The precipitate was a dioxime derivative of lambda-carrageenan.



diketone dioxime derivative

ANAL: Dioxime derivative of lambda-carrageenan $C_{12}H_{13}O_{20}N_2S_3$ (601): Calcd. (found): C, 23.96 (23.75); H, 2.16 (2.18); N, 4.66 (4.33). 1670 (C=N); IR: 3325-3355 (OH of COOH and oxime); 1240 cm^{-1} (C—O—C of lambda-CAR), and 1685 (C=O of COOH).

Fourier transform spectra (FTIR)

The FTIR spectra were recorded using the Pye-Unicam Sp 3100 described earlier [18-22]. The KBr was used as a blank background within a resolution of 4.0 cm-1 and the wavenumber of the range 4000-200 cm^{-1}, as indicated in **Figure 2**.

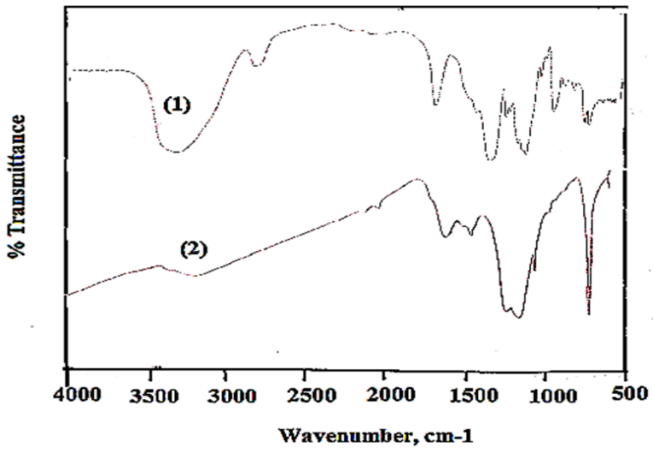


Figure 2. FTIR spectra of: (1): λ-CAR and (2): Keto-Acid-λ-CAR sulfated polysaccharide

RESULTS AND DISCUSSION

Reaction stoichiometry

The oxidation of lambda-carrageenan by alkaline MnO^-_4 was obedience to the following stoichiometric equations,

$$3\,(C_{12}\,H_{17}\,O_{19}\,S_3)^{3-}{}_n + 8\,MnO_4^- = 3\,(C_{12}\,H_{11}\,O_{20}\,S_3)^{3-}{}_n + 8\,MnO_2 + 8\,OH^- + 5\,H_2O \quad (1)$$

where $(C_{12}\,H_{17}\,O_{19}\,S_3)^{3-}{}_n$ and $(C_{12}\,H_{11}\,O_{20}\,S_3)^{3-}{}_n$ are LCAR and its keto- acid oxidation derivative precursor, respectively.

This oxidation derivative precursor was confirmed by forming dioxime derivatives and bis-2,4-dinitrophenyl hydrazone when reacted with hydroxylamine and 2,4-dinitrophenylhydrazine, respectively. The yield was 96.2%.

The behavior of oxidation reaction progression

It has been found that the LCAR substrate oxidation by alkaline permanganate ion in alkaline media was proceeding via two remarkable separated stages. The first one was relatively fast with and accompanied by the formation of detectable coordination biopolymer intermediate complexes including transient species of green manganate (VI) [LCAR-$Mn^{VI}O_4^{2-}$] and blue hypomanganate (V) [LCAR-$Mn^{V}O_4^{3-}$] [25-28]. This reaction has proven a base-catalyzed oxidation nature. When these intermediates were built up, the formed intermediated complexes started to decay slowly for giving the final oxidation products. **Figure 3** indicates the spectra change during the reaction progression. A conventional spectrophotometer was used to detect such formed blue hypomanganatethe (V) intermediate for the first time **(Figure 4)**. The formation and decomposition of the intermediate complex during the oxidation reaction progression are shown in **Figure 5**.

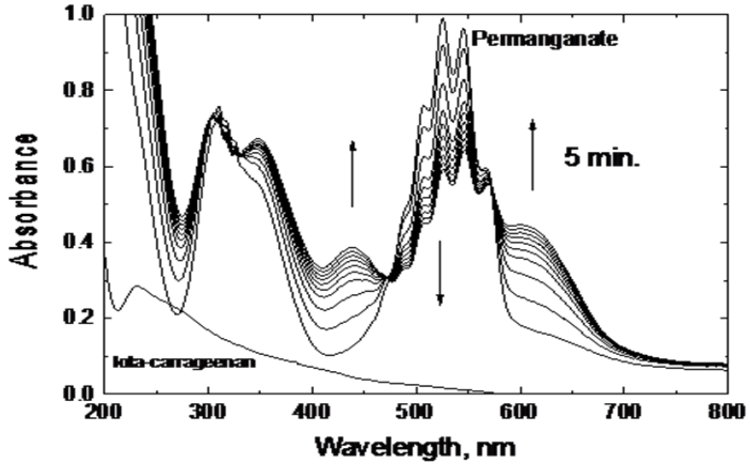


Figure 3. Spectral changes during the formation of intermediate complexes in the oxidation of lambda- carrageenan by alkaline permanganate. [MnO_4^-] = $4x10^{-4}$, [LCAR] = $4x10^{-3}$ and I = 0.1 mol dm^{-3} at 25° C.

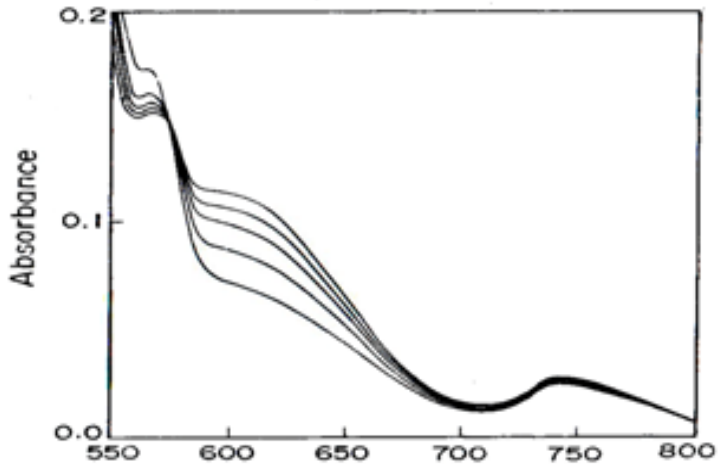
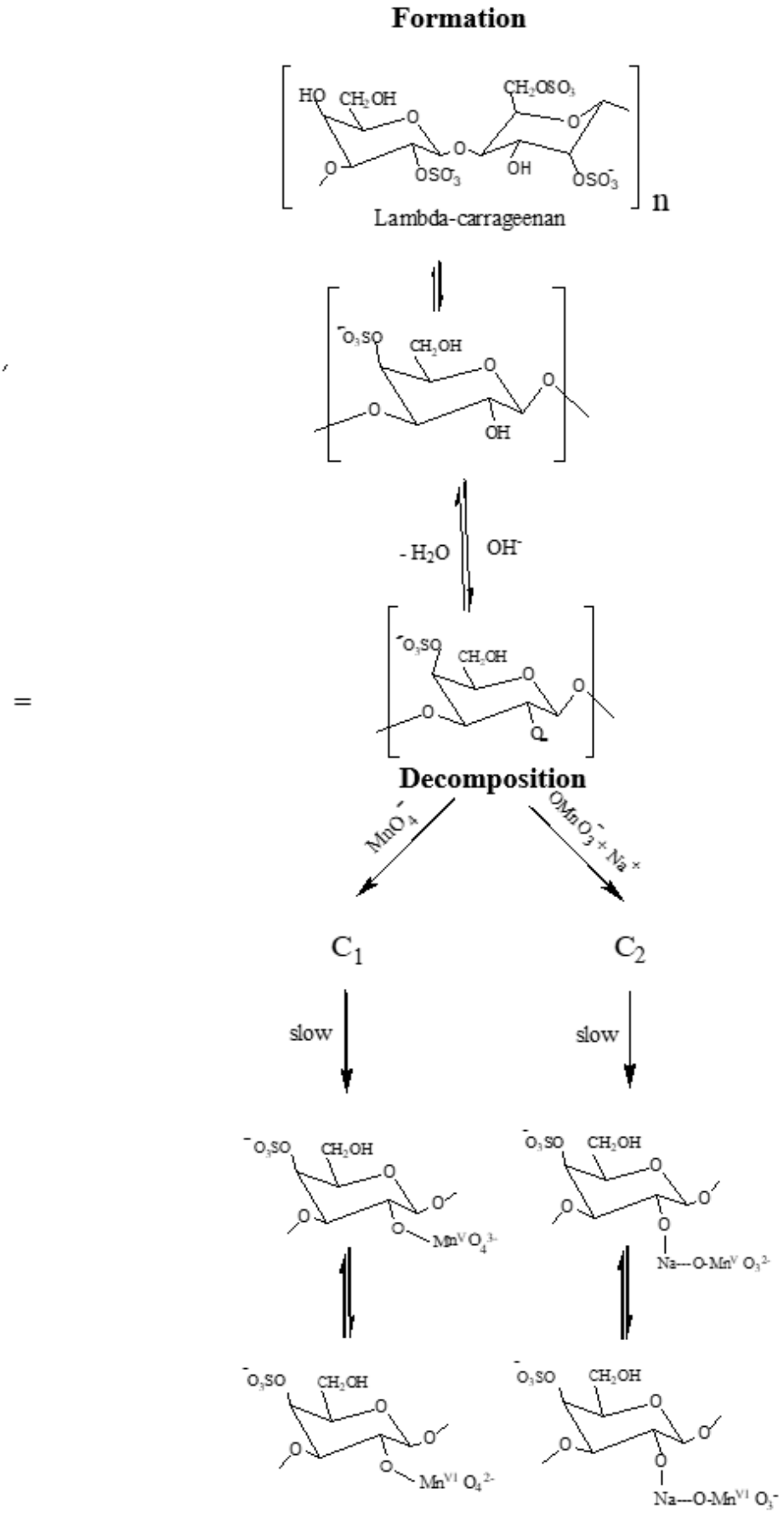


Figure 4. Formation of green mamganate(VI) and blue hypomanganate (V) at wavelengths of ~ 610 and ~750 $cm^{-1,}$ respectively, during the oxidation of lambda-carrageenan by permanganate ion at [MnO_4^-] =$1x10^{-4}$, [LCAR] =$4x10^{-3}$, [OH^-]=0.05, I=0.1 $moldm^{-3}$ < 10°C.


Formation
Lambda-carrageenan
n
- H2O
OH-
=
Decomposition
MnO4-
OMnO3- + Na+
C1
C2
slow
slow

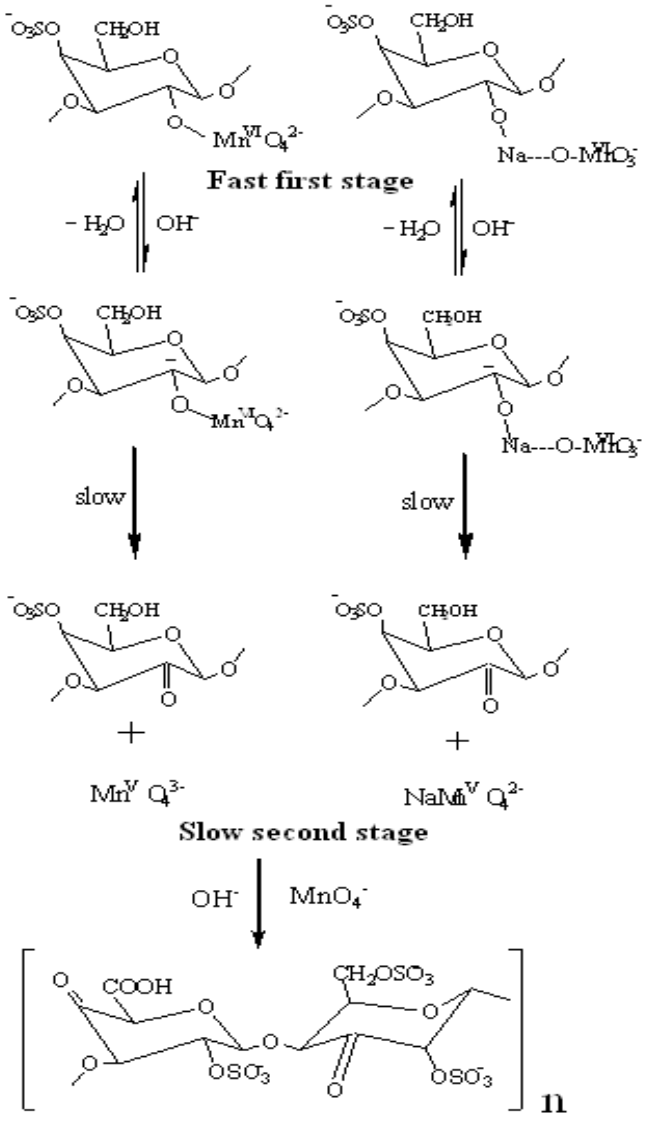


Figure 5. The formation and decomposition of the coordination biopolymer intermediate complex during the oxidation of LCAR by alkaline permanganate.

CONCLUSION

Novel diketo-LCAR has been synthesized by lambda-carrageenan oxidation as sulfated polysaccharide by permanganate ion in alkaline media at pH`s > 12 for the first time. FTIR spectroscopy and elemental analysis characterized the precursor oxidation product using 2,4-dinitrophenyl hydrazine and hydroxyl amine, which affords the formation of its corresponding 2,4-dinitrophenyl hydrazone and dioxime derivatives, respectively. This product can be applied effectively in pharmaceutics, medicine, biomedicine, and food industries such as a carrier in drug delivery, fiber formulation in pharmaceutics, lipids as stiffening bind materials, and food dietary industrial applications. In addition, it can be used to prevent diabetes complications, suppress hyperglycemia, reverse insulin resistance, antiviral, antibacterial, anticoagulant, antioxidant, and antitumor. This may be attributed to its high anti-diabetic activity. This is in addition to the applications as a carrier in drug delivery for Ca(II) for patients suffering from Ca (II) deficiency or coarseness bones since it has high affinity for chelation with divalent metal ions.

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Ethics statement: None

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