SMER
SOCIETY OF MEDICAL
EDUCATION & RESEARCH

Society of Medical Education & Research

2021, Volume 1, Page No: 34-40
ISSN: 3108-4826

Journal of Medical Sciences and Interdisciplinary Research

Development of a New Keto Acid Precursor for Lambda-Carrageenan Oxidation via Alkaline Permanganate

Refat M. Hassan[1*]

[1] Department of Chemistry, Faculty of Science, Assiut University, Assiut 71516, Egypt.

***E-mail** ✉ rmhassan2002@yahoo.com

Abstract

The present study aimed at developing a new keto acid precursor for the oxidation of lambda-carrageenan via alkaline permanganate. A new class of keto-acid derivatives of lambda-carrageenan (LCAR), in the form of sulfated polysaccharides, was synthesized by oxidizing LCAR with permanganate ions in an alkaline environment at pH levels greater than 12. The reactants MnO4-, LCAR, and NaF were combined in precise stoichiometric ratios in alkaline solutions with pH values above 12. The mixture was stirred for approximately 48 hours to complete the reaction. The resulting colloidal precipitate of MnF4 was separated via filtration. The filtrate was then concentrated to approximately one-fifth of its initial volume using a rotary evaporator, followed by acidification with acetic acid to a pH range of 5-6. Vacuum evaporation was used to remove excess moisture, and the product was stored aside for future use. The oxidation product was confirmed using hydroxyl amine and 2,4-dinitrophenyl hydrazine, leading to the construction of the corresponding 2,4-dinitrophenyl hydrazone and dioxime derivatives. These results indicate the successful synthesis of ketoacid-LCAR as the final oxidation product. This innovative oxidation product shows great potential for applications in pharmaceuticals, medicine, biomedicine, and the food industry.

Keywords: Synthesis, Ketoacid LCAR, Pharmaceuticals, Biomedicine

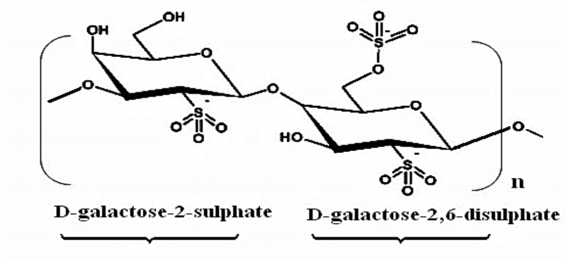
Introduction

Carrageenans (CAR) are linear, sulfated, water-soluble polysaccharides obtained from particular species of red algae. These molecules are made up of repeating disaccharide units, which are composed of galactose and 3,6-anhydrogalactose. The carrageenan family includes various types, such as kappa (KCAR), iota (ICAR), and lambda (LCAR), all of which are typically connected by glycosidic bonds [1, 2]. The structural arrangement of LCAR is shown in **Figure 1**.

Access this article online https://smerpub.com/

Received: 29 May 2021; **Accepted:** 01 September 2021

How to cite this article: Hassan RM. Development of a New Keto Acid Precursor for Lambda-Carrageenan Oxidation via Alkaline Permanganate. J Med Sci Interdiscip Res. 2021;1:34-40. https://doi.org/10.51847/64qDGaqweV



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

Figure 1. Configuration structure of LCAR

Lambda-carrageenan (LCAR), a polysaccharide, is gaining attention as a promising candidate for use in the pharmaceutical, medical, biotechnological, and food industries. Its diverse applications include pharmaceutical products like toothpaste, air fresheners, firefighting foams, shampoos, and cosmetic creams, as well as tissue engineering, food processing, and drug delivery systems [3-5]. This is largely due to LCAR's remarkable bioactive properties, including anticoagulant, antioxidant, antiviral, antibacterial, antitumor, and immune-modulating effects [4, 6, 7]. These characteristics are supported by its favorable physical traits such as biodegradability, biocompatibility, non-toxicity, hydrophilicity, environmental friendliness, and cost-effectiveness.

The macromolecular structure of LCAR contains functional groups like hydroxyl, carboxylate, and sulfate within its backbone, contributing to its high solubility in water and its ability to form gels. Additionally, polysaccharides are recognized as strong reducing agents, which allows LCAR to decrease the permanganate ion (VII), a powerful oxidizing agent, in both acidic and alkaline environments. This reduction results in the formation of Mn(II) or Mn(IV) species, alongside the oxidation of LCAR, to produce either ketoacid or ketoaldehyde derivatives, depending on the experimental conditions, like solvent type, oxidant, and pH [8-23]. The present study aimed to develop a new keto acid precursor for the oxidation of lambda-carrageenan via alkaline permanganate.

Materials and Methods

Materials

The lambda-carrageenan (L-CAR) used in this study was sourced from Fluka Reagents and was used without additional purification.

Preparation of LCAR solution

The preparation of the LCAR solution followed the procedure outlined in previous studies [24, 25]. All other materials used in the experiments were of analytical grade. Distilled water was used for all preparations.

Synthesis of Keto-Acid Oxidation Derivative of Sulfated Lambda-Carrageenan (LCAR)

Five grams of LCAR powder were dissolved in 350 cm^3 of deionized water, and the pH was adjusted to ≥ 12 using NaOH. The powder was added gradually to the solution when constantly stirring to prevent clumping and ensure uniform dissolution [24, 25]. A stepwise addition of 150 cm^3 of a solution containing 5.43 g of NaF and 5.17 g of MnO_4^- was introduced over 2 hours. The mixture was then stirred at 25 degrees for approximately 48 hours to allow the reaction to complete. The resulting colloidal MnF_4 solution was filtered to separate the solid. The filtrate was concentrated to one-fifth of its original volume using a rotary evaporator. The concentrated solution was acidified to a pH of approximately 5-6 using dilute acetic acid. The final was dried under vacuum and subjected to elemental analysis and IR spectroscopy.

The detailed mechanism and kinetics of LCAR oxidation by alkaline permanganate are discussed in earlier works [25, 26].

Polymerization Test

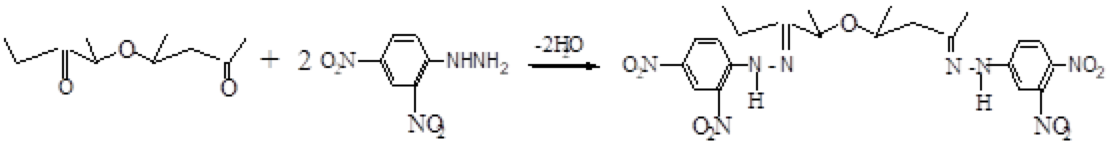
To assess the involvement of free radicals in the process of oxidation, acrylonitrile was introduced into the partially oxidized mixture. The absence of polymerization confirmed that free radicals did not participate in the reaction.

Identifying the Oxidation Product

The oxidation products were detected using 2,4-dinitrophenylhydrazine and hydroxylamine based on previously established methods [20-27].

Usage of 2,4-Dinitrophenylhydrazine

A diketone solution was mixed with a 2,4-dinitrophenylhydrazine solution and heated in a water bath. This led to the formation of a yellow precipitate, confirming the presence of the hydrazone derivative of LCAR.



diketone

2,4-dinitrophenyl hydrazone derivative

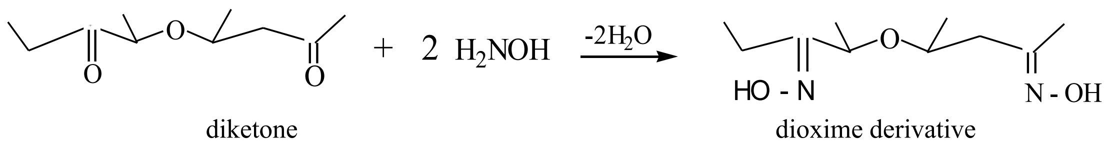
Analytical data

The 2,4-dinitrophenylhydrazone derivative of lambda-carrageenan (C24H19O26N8S3) showed the following analytical results:

Calculated: C, 30.93 (30.96); H, 2.05 (2.01); N, 12.03 (12.12).
IR Peaks: 3320 cm^{-1} (NH of hydrazone), 3415 cm^{-1} (OH of COOH group), 1262 cm^{-1} (C—O—C of LCAR), and 1660 cm^{-1} (C=N of hydrazone).

Hydroxylamine reaction

Upon heating the diketone solution with hydroxylamine in a water bath, a white precipitate formed, which was identified as the dioxime derivative of lambda-carrageenan.



Dioxime derivative: C12H13O20N2S3

Calculated: C, 23.96 (23.75); H, 2.16 (2.18); N, 4.66 (4.33).
IR Peaks: 1670 cm^{-1} (C=N), 3325-3355 cm^{-1} (OH of COOH and oxime), 1240 cm^{-1} (C—O—C of LCAR), and 1685 cm^{-1} (C=O of COOH).
Fourier Transform Infrared Spectroscopy (FTIR):
FTIR spectra were obtained with the Pye-Unicam Sp 3100, with KBr serving as a background. The resolution was set to 4.0 cm^{-1}, and spectra were recorded within the wavenumber range of 4000-200 cm^{-1}, as shown in **Figure 2**.
Fourier Transform Infrared Spectroscopy (FTIR):
The FTIR spectra were collected with the Pye-Unicam Sp 3100, as outlined in previous studies [18-22]. KBr was utilized as a background reference, with a resolution of 4.0 cm^{-1} and a wavenumber range of 4000-200 cm^{-1}, as shown in **Figure 2**.

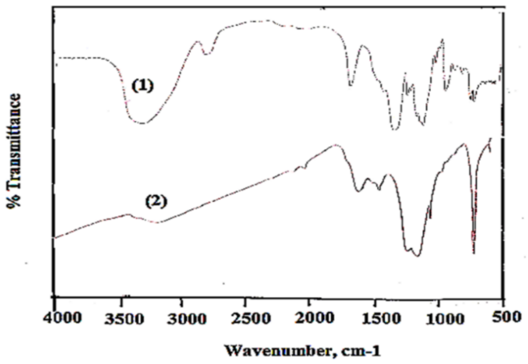


Figure 2. FTIR spectra of: (1): λ-CAR and (2): Keto-Acid-λ-CAR sulfated polysaccharide

Results and Discussion

Stoichiometric analysis

The oxidation of lambda-carrageenan using alkaline MnO_4^- followed the stoichiometric equation as shown below:

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

In this equation, (C12 H17 O19 S3)3-n represents LCAR, while (C12 H11 O20 S3)3-n is the keto-acid derivative formed as a result of the oxidation process. The formation of this derivative was confirmed by reactions with hydroxylamine and 2,4-dinitrophenylhydrazine, which produced the corresponding dioxime and bis-2,4-dinitrophenylhydrazone derivatives. The yield of this oxidation process was found to be 96.2%.

Oxidation reaction dynamics

The oxidation of LCAR by alkaline permanganate in basic media occurred in two distinct phases. The initial stage was relatively fast and involved the detectable formation of biopolymer complexes, including transient species such as the green manganate (VI) complex [LCAR-$MnVIO_4^{2-}$] and the blue hypomanganate (V) complex [LCAR-$MnVO_4^{3-}$] [25-28]. This phase indicated that the oxidation followed a base-catalyzed mechanism.
As the reaction progressed, these intermediate complexes slowly decomposed, leading to the final products. **Figure 3** illustrates the spectral changes throughout the reaction, while **Figure 4** demonstrates the detection of the blue hypomanganate (V) intermediate using a conventional spectrophotometer. The formation and eventual decomposition of the intermediate complexes during the oxidation process are further depicted in **Figure 5**.

Oxidation Reaction Progression

The oxidation of the LCAR substrate by alkaline permanganate in basic media was observed to proceed in two distinct stages. The initial stage occurred rapidly and was accompanied by the forming of intermediate complexes detected, including transient species such as the green manganate (VI) complex $[\mathrm{LCAR\text{-}MnVIO_4^{2-}}]$ and the blue hypomanganate (V) complex $[\mathrm{LCAR\text{-}MnVO_4^{3-}}]$ [25-28]. This indicated that the reaction followed a base-catalyzed oxidation mechanism.

As the reaction continued, these intermediate complexes gradually decomposed, leading to the formation of the final oxidation products. The changes in spectra during the reaction can be seen in **Figure 3**, which tracks the progression. A conventional spectrophotometer was employed to detect the blue hypomanganate (V) intermediate, a first-time observation as shown in **Figure 4. Figure 5** illustrates the formation and subsequent decay of the intermediate complex throughout the oxidation process.

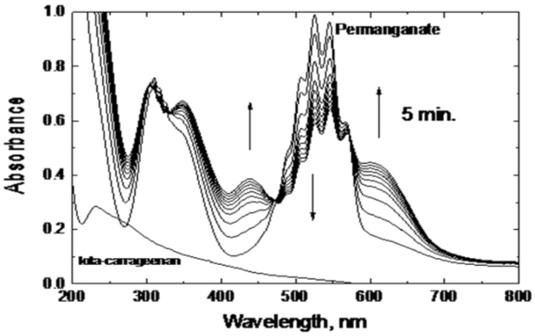


Figure 3. Spectral changes during the formation of intermediate complexes in the oxidation of lambda-carrageenan by alkaline permanganate. $[\mathrm{MnO_4^-}] = 4 \times 10^{-4}$, $[\mathrm{LCAR}] = 4 \times 10^{-3}$ and $I = 0.1$ mol dm^{-3} at 25 °C.

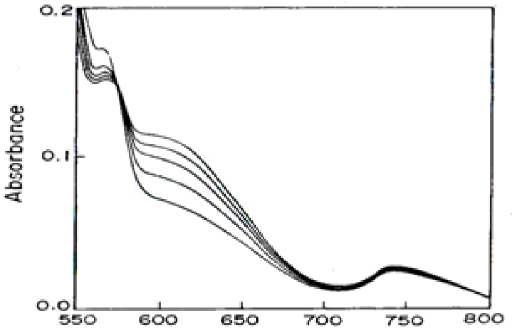
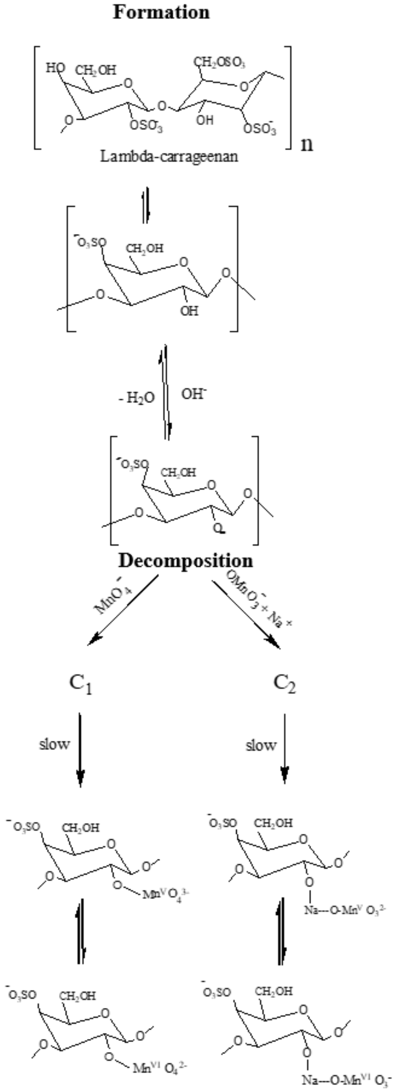


Figure 4. Formation of green mamganate (VI) and blue hypomanganate (V) at wavelengths of ~ 610 and ~750 cm^{-1}, respectively, during the oxidation of lambda-carrageenan by permanganate ion at $[\mathrm{MnO_4^-}] = 1\times10^{-4}$, $[\mathrm{LCAR}] = 4\times10^{-3}$, $[\mathrm{OH^-}] = 0.05$, $I = 0.1$ moldm^{-3} < 10 °C.



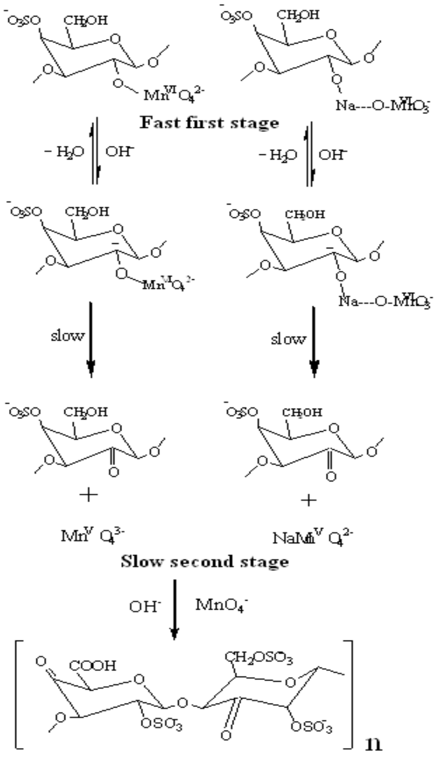


Figure 5. The formation and decomposition of the coordination biopolymer intermediate complex during the oxidation of LCAR by alkaline permanganate.

Conclusion

A new diketo-LCAR compound was successfully synthesized by oxidizing lambda-carrageenan, a sulfated polysaccharide, using permanganate ion in an alkaline environment with a pH exceeding 12. The oxidation product was confirmed through FTIR spectroscopy and analysis, with 2,4-dinitrophenylhydrazine and hydroxylamine proving the formation of its corresponding 2,4-dinitrophenyl hydrazone and dioxime derivatives. This innovative compound shows considerable promise for use in pharmaceuticals, medicine, biomedicine, and the food industry. It can be utilized in drug delivery systems, as a fiber component in pharmaceutical formulations, and as a stiffening agent in lipid-based materials for food production. Additionally, it has demonstrated beneficial effects in combating diabetes-related complications, managing hyperglycemia, improving insulin sensitivity, and offering antiviral, antibacterial, antioxidant, anticoagulant, and anticancer activities. Its strong anti-diabetic properties, coupled with its ability to chelate divalent metal ions like Ca(II), make it a potential treatment for individuals with calcium deficiencies or fragile bones.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Li L, Ni R, Shao Y, Mao S. Carrageenan and its applications in drug delivery. Carbohydr Polym. 2014;103:1-11.
2. Davidson RL. Handbook of Water-Soluble Gums and Resins. McGraw-Hill; New York, Chapter 5. 1980.
3. Guan J, Li L, Mao S. Applications of Carrageenan in Advanced Drug Delivery. Chapter 15, in the Book entitled "Seaweed Polysaccharides," Edited by J. Venkatesan and S. Aril, 1st Edn, Elsevier; 2017. pp.283-303.
4. Pacheco-Quito EM, Ruiz-Caro R, Veiga MD. Carrageenan: Drug Delivery Systems and Other Biomedical Applications. Mar Drugs. 2020;18(11):583-613.
5. Pettinelli N, Rodríguez-Llamazares S, Bouza R, Barral L, Feijoo-Bandín S, Lago F. Carrageenan-based physically crosslinked injectable hydrogel for wound healing and tissue repairing applications. Int J Pharm. 2020;589:119828.
6. Necas J, Bartosikova L. Carrageenan: a review. Vet Med. 2013;58(4):187-205.
7. Wijesekara I, Pangestuti R, Kim SK. Biological activities and potential health benefits of sulfated polysaccharides derived from marine algae. Carbohydr Polym. 2011;84(1):14-21.
8. Fatiadi AJ. The classical permanganate ion: still a novel oxidant in organic chemistry. Synthesis. 1987;1987(02):85-127.
9. Lee DG. The oxidation of organic compounds by permanganate ion and hexavalent chromium. Open Court Publishing Company; 1980.

10. Moore FM, Hicks KW. Mechanism of the permanganate ion oxidation of vanadium (IV). Inorg Chem. 1975;14(2):413-6.
11. Rawoof MA, Sutter JR. Kinetic studies of permanganate oxidation reactions. II. Reaction with ferrocyanide ion. J Phys Chem. 1967;71(9):2767-71.
12. Hassan RM, Mousa MA, El-Shatovry SA. Kinetics of oxidation of uranium (IV) by permanganate ion in aqueous perchlorate media. J Chem Soc, Dalton Trans. 1988(3):601-3.
13. Hassan RM. Alginate polyelectrolyte ionotropic gels. XIV. Kinetics and mechanism of formation of intermediate complex during the oxidation of alginate polysaccharide by alkaline permanganate with a spectrophotometric evidence of manganate (VI) transient species. J Polym Sci A Polym Chem. 1993;31(1):51-9.
14. Khairou KS, Hassan RM. Pectate polyelectrolyte ionotropic gels: 1. Kinetics and mechanisms of formation of manganate (VI)–pectate intermediate complex during the oxidation of pectate polysaccharide by alkaline permanganate. Eur Polym J. 2000;36(9):2021-30.
15. Khairou KS. Kinetics and mechanism of decomposition of intermediate complex during oxidation of pectate polysaccharide by potassium permanganate in alkaline solutions. Int J Chem Kinet. 2003;35(2):67-72.
16. Hassan RM. New coordination polymers. III: Oxidation of poly (vinyl alcohol) by permanganate ion in alkaline solutions. Kinetics and mechanism of formation of intermediate complex with a spectrophotometric detection of manganate (vi) transient species. Polym Int. 1993;30(1):5-9.
17. Hassan R, Ibrahim S, Sayed S. Kinetics and mechanistic aspects on electron-transfer process for permanganate oxidation of poly (ethylene glycol) in aqueous acidic solutions in the presence and absence of Ru (III) catalyst. Int J Chem Kinet. 2018;50(11):775-83.
18. Hassan RM, Abd-Alla MA, El-Zohry MF. Alginate polyelectrolyte ionotropic gels. VI. Novel synthesis of diketoalginates as biopolymer precursors. J Appl Polym Sci. 1993;47(9):1649-52.
19. Hassan RM, Abd-Alla MA. New coordination polymers. Part 1.—Novel synthesis of poly (vinyl ketone) and characterization as chelating agent. J Mater Chem. 1992;2(6):609-11.
20. Hassan RM, Ibrahim SM, Khairou KS. Novel synthesis of diketopectate coordination biopolymer derivatives as alternative promising in biomedicine, pharmaceutics and food Industrial applications. J Nutr Food Process. 2019;2:1-5.
21. Khairou KS, Hassan RM, Shaker AM. Novel synthesis of diketocarboxymethyl-celluose as bipolymer precursors. J Appl Polym Sci. 2002;85(5):1019-23.
22. Hassan RM, Ibrahim SM. Novel synthesis of coordination biopolymer precursor from oxidation of methyl cellulose by alkaline potassium permanganate. Integr Food Nutr Metab. 2019;6:1-5.
23. Zaafarany I, Gobouri A, Hassan R. Oxidation of some sulfated carbohydrates: kinetics and mechanism of oxidation of chondroitin-4-sulfate by alkaline permanganate with novel synthesis of coordination biopolymer precursor. J Mater Sci Res. 2013;2(4):23-35.
24. Fawzy A, Zaafarany IA, Althagafi II, Alfahemi JH, Altass HM, Khairou KS,et al.. Synthesis of Novel Diketoacid Carragenans as Coordination Biopolymeric Chealting Agent Precursor by Oxidation of Kappa-Carrageenan Polysaccharide by Alkaline Permanganate. Am Assoc Sci Technol. 2016;3:49-55.
25. Hassan RM, Fawzy A, Ahmed GA, Zaafarany IA, Asghar BH, Takagi HD,et al.. Kinetics and mechanism of permanganate oxidation of iota-and lambda-carrageenan polysaccharides as sulfated carbohydrates in acid perchlorate solutions. Carbohydr Res. 2011;346(14):2260-7.
26. Hassan RM, Ibrahim SM, Fawzy A. Novel synthesis of coordination bipolymer precursors of sulfated macromolecules as alternative promising in biomedicine, pharmaceutics and engineering industry by oxidation of sustainable and biodegradable sulfated iota-carrageenan, by alkaline permanganate. J Nanomed. 2020;3:1026.
27. Hassan RM, Fawzy A, Alarifi A, Ahmed GA, Zaafarany IA, Takagi HD. Base-catalyzed oxidation of some sulfated macromolecules: kinetics and mechanism of formation of intermediate complexes of short-lived manganate (VI) and/or hypomanganate (V) during oxidation of iota-and lambda-carrageenan polysaccharides by alkaline permanganate. J Mol Catal A Chem. 2011;335(1-2):38-45.

28. Ahmed GA, Fawzy A, Hassan RM. Spectrophotometric evidence for the formation of short-lived hypomanganate (V) and manganate (VI) transient species during the oxidation of K-carrageenan by alkaline permanganate. Carbohydr Res. 2007;342(10):1382-6.