International Journal of Bio-Science and Bio-Technology
Vol.8, No.1 (2016), pp.339-350
http://dx.doi.org/10.14257/ijbsbt.2016.8.1.30

Synthesis and Characterization of 1-octyl 2-cyano Acrylate for Wound Healing Applications

Rajangam Vinodh[1], Cadiam Mohan Babu[1], Aziz Abidov[1], Rramaswamy Ravikumar[1], Muthiahpillai Palanichamy[1], Eun Young Choi[2] and Hyun Tae Jang[1*]

[1]*Department of Chemical Engineering, Hanseo University, Seosan 360-706, South Korea*
[2] *Department of Cosmatology, Hanseo University, Seosan 360-706, South Korea*
htjang@hanseo.ac.kr

Abstract

Cyanoacrylate glues are quick setting materials which rapidly cure to hard, clear glassy resins. Its synthesis too has not been reported in the open literature so far. Synthetic methods, which engage esterification of cyanoacetic acid with a preferred alcohol, polymerization by knoevenagel condensation and successive depolymerization, are applied to the synthesis of lower membered alkyl cyanoacryaltes in which the alkyl groups carry less than 8 carbons. We have synthesized 1-octyl cyanoacetate by a traditional method involving p-toluene sulphonic acid as the catalyst. In the second step, we have attempted the preparation of poly (n-octyl cyanoacrylate) by the reaction of formaldehyde with n-octyl-2-cyanoacetate in the presence of both piperidine and potassium carbonate in the absence of any solvents. Its FTIR spectrum confirmed its functional groups: Its –OH stretching yielded a broad band around 3400 cm^{-1}. The polymer was depolymerized using poly phosphoric acid catalyst under vacuum to obtain the monomer. A simple method of obtaining monomer was also attempted by the reaction of 1-octyl- 2-cyano acetate and diiodomethane in the presence of potassium carbonate. This process directly yields the monomer. The second method looks better than the others, and it can be applied to any type of alcohols.

Keywords*: Wound adhesive, cyanoacrylate, depolymerization, cyanoacetic acid*

1. Introduction

Wound closure techniques have evolved from the earliest development of suturing materials to resources that include synthetic absorbable sutures, staples, tapes, and adhesive compounds. The creation of natural glues, surgical staples and tapes to substitute sutures has supplemented the armamentarium of wound closure techniques. The use of tissue adhesives has long appealed to surgeons and they have been extensively studied for nearly four decades for diverse applications including tissue adhesion, wound closure, hemostasis, and closure of cerebrospinal fluid (CSF) leaks, vascular embolization and application of skin grafts [1].

The ideal method of laceration and incision closure should be simple, safe, rapid, inexpensive, painless, bactericidal, and result in optimal cosmetic appearance of the scar. The cyanoacrylate tissue adhesives offer many of these characteristics. Developed in 1949, the cyanoacrylate adhesives are applied topically to the outermost skin layer. The cyanoacrylates are supplied as monomers in a liquid form. On contact with tissue anions,

ISSN: 2233-7849 IJBSBT

they polymerize forming a strong bond that holds the apposed wound edges together. The cyanoacrylate adhesives usually slough off with wound re-epithelialization within 5–10 days and do not require removal.

The use of cyanoacrylate has increased significantly in recent years owing to their unique combination of chemical and physical properties, namely; (i) they cure rapidly ambient temperature, (ii) they form strong bonds with a wide variety of different materials without the addition of a catalyst, (iii) they can be easily and safely applied either manually or by automatic equipment, and (iv) they are ready to use without mixing or using a primer [2].

In modern times, with the advent of elective surgery, more energy has been directed at achieving an efficient and uncomplicated healing of the deliberately inflicted wound. "Never judge the surgeon until you have seen him closing the wound" is a saying attributed to Lord Moynihan. The surgical scar remains the only visible evidence of the surgeon's skill and not infrequently, all of his efforts are judged on its final appearance. Advances in anesthesia and surgery have not been paralleled by advances in wound care, which is an integral part of any surgical procedure. The method of skin closure generally used in surgery is with sutures which provide an extra source of contamination and are a potential source of foreign body reaction in the susceptible subcutaneous tissue [3, 4]. This increases the complication rate besides being time consuming during application. To overcome these shortcomings, various methods of skin closure have been tried which include stapling and adhesive tapes, but none have been found to be effective.

The cyanoacrylate adhesives are characterized by rapid curing, strong bonding of even different surfaces and easy handling. The monomer cyanoacrylate is difficult to prepare directly, but only obtained via depolymerization of poly (cyanoacrylate). The acrylates were first synthesized by Ardis in 1949 [5]. Coover et al discovered adhesive properties of acrylates and suggested their use as surgical adhesives [6]. The first commercial adhesive based on methyl 2-cyanoacrylate, Eastman 910, appeared in 1958. Similar adhesive compositions later appeared as Krazy glue (ethyl 2-cyanoacrylate), Super glue, Permabond etc. in the market. There are many reports on cyanoacrylates in the literature but mostly are patents. The industrial synthesis of cyanoacrylate monomers is based on Knoevenagel condensation of 2-cyano acetate and formalin in the presence of a basic catalyst to form a polymer. The polymer is subsequently depolymerized to obtain the monomer. The monomer requires subsequent purification. The high temperatures required for cracking the polymers limit the synthetic diversity and the number of different side chains that can be incorporated into a cyanoacrylate prepared using this method. Accordingly, the diversity of cyanoacrylate monomers prepared industrially is quite limited. A German patent [7] discloses thermolysis of a particular acrylate polymer between 300 and 800 °C. A US patent [8] communicates a synthetic method for the production of alpha-cyanoacrylate esters by means of trans-esterification of an existing alpha-cyanoacrylate monomer. The substrate diversity of this method is limited on account of the harsh trans-esterification step. While the reaction between formaldehyde and cyanoacetate can be carried out without the use of an added solvent since the formaldehyde starting material is liquid under reaction conditions, it has been found to be more desirable to use a solvent during the polymerization reaction. Normally these solvents have been relatively low boiling liquids and are expelled before depolymerization.

Sutures have conventionally been the method of approximating wound edges due to their high tensile strength and favorable cosmetic outcomes. Sutures do, however, have some downfalls in that they require increased time and a skilled individual to accomplish good cosmetic outcomes. Over the past four decades, advances have seen other forms of wound closure methods emerge that address some of the disadvantages of sutures [9-14].

Similarly, the usefulness of a high boiling liquid during the second stage in the preparation of monomeric alpha-cyanoacrylates, i.e., during depolymerization of polymeric cyanoacrylate, has been recognized. So, phosphate which boils at a temperature above the de-polymerization temperature of the polymeric material is suggested. The high boiling material has the effect of improving heat transfer within the depolymerization reaction mixture and thus, advantageously, lowers the temperature to which the polymer mass must be heated before depolymerization occurs. In the present study 1-octyl cyanoacetate was separately synthesized in our lab and characterized, although it is commercially available. Its conversion to poly (1-octyl cyanoacrylate) and its subsequent catalytic depolymerization to 1-octylcyanoacrylate were conducted in the absence of any solvents. The parent ester, polymer and monomer were separately characterized by common analytical techniques FTIR and TGA and the results discussed. Schematic representation of wound healing adhesive applied on the human skin was represented in the Figure 1.

Figure 1. Schematic Illustration of Synthesized Adhesive to Cure Skin Wound Healing

2. Experimental

2.1 Materials

The name of chemicals used in this study was tabulated in the following Table 1 with manufactures.

Table 1. Name of Chemicals used in this Study and Their Source

S. No.	Chemicals	Sources
1	Cyanoacetic acid	Sigma Aldrich, USA
2	Toluene	Sam Chun, South Korea
3	*P*-toluene sulphonic acid	Daejung, South Korea
4	1-octanol	Sigma Aldrich, USA
5	Poly phosphoric acid	Sigma Aldrich, USA
6	Phosphorous pentoxide	Sam Chun, South Korea
7	30% Formaldehyde solution	Sam Chun, South Korea
8	Piperidine	Daejung, South Korea
9	Potassium carbonate	Daejung, South Korea
10	Acetic acid	Sam Chun, South Korea

2.2 Synthesis of 1-octyl Cyano Acrylate

It involves three stages, such as,

(i) Preparation of 1-octyl cyano acetate,
(ii) Preparation of poly (1-octyl cyanoacrylate) and
(iii) Preparation of 1-octyl cyanoacrylate.

The brief synthesis protocol was discussed in the manuscript as follows.

2.3 Preparation of 1-Octyl Cyano Acetate

17.8 g cyanoacetic acid, 26 g 1-octanol, 0.5 g p-toluene sulphonic acid and 80 mL toluene were taken in a 250 mL RB flask. It is attached to a Dean-stark trap which in turn attached to a water condenser. The contents of the flask were heated to 135 °C under stirring for 5 h. Water formed in this esterification was removed by forming azeotrope with toluene in order to complete esterification. The total amount of water collected in the trap was equal to 3.6 g. The RB flask was cooled and the contents were filtered through a Buchner funnel. The filtrate in the Buchner flask was treated with 25 mL of 10 g $NaHCO_3$ solution, shaken well and transferred to a 250 mL separating funnel. It was allowed to stand until the organic and aqueous layers were separated. The lower aqueous layer was discarded and the upper organic layer transferred to the Buchner flask. It is again treated with another 25 mL of $NaHCO_3$ solution and process was repeated. Finally the liquid was washed twice with 25 mL of water and dried over anhydrous $MgSO_4$ for 3h. It was then filtered through a Buchner funnel and the toluene in the filtrate vacuum evaporated. Note the yield of 1-octyl cyanoacetate.

2.4 Preparation of Poly (1-Octyl Cyanoacrylate)

8 g of 1-octyl cyanoacrylate was taken in a 100 mL beaker. 3.5 g formalin and 0.1 g of potassium carbonate were added to it. The mixture was stirred vigorously on a magnetic stirrer for 12 h. A white thick poly (1-octyl cyanoacryalte) was obtained.

The polymer was dissolved in 100 mL of acetone and n-hexane mixture (2:1 wt%) and transferred to a 250 mL conical flask. 25 mL of 5% HCl was added to it and shaken well. The organic layer was separated using a separating funnel and the procedure was repeated with another 25 mL of dil. HCl. The resulting organic layer was transferred to a clean conical flask. 5g of anhydrous magnesium sulphate was added to it, shaken well and allowed to stand for 1 h. It was then filtered and the filtrate in a 250 mL RB flask was subjected to vacuum distillation to recover the polymer.

2.5 Preparation of 1-Octyl Cyanoacrylate

The above polymers synthesized with potassium carbonate and piperidine were separately treated with 0.1 g of poly phosphoric acid, 0.5 g of P_2O_5 and 0.1 g of hydroquinone and subjected to thermal depolymerization between 120 and 210 °C raised in steps of 20 °C. The depolymerization was also conducted in the absence of the above reagents. The product was collected at each temperature and characterized by FTIR.

2.6 Fourier Transform Infra Red Spectroscopy

The chemical structure of the prepared materials was analyzed using FTIR. The FTIR spectra were recorded in transmission mode using Perkin Elmer spectrometer by placing the membranes in KBr windows (4000 to 400 cm^{-1}).

2.7 Thermogravimetric Analysis

This is the technique in which the change in weight of a substance with temperature over a period of time is followed. Thermal stability and decomposition temperature of the polymer can be assessed easily using this technique. The TGA thermal analysis was carried out using TGA model Q50 V20.6 build 31 systems. The measurements were conducted by heating from room temperature to 800 °C at a heating rate of 10 °C/min under nitrogen atmosphere.

3. Results and Discussion

Figure 2 shows the FTIR spectrum of 1-octyl cyanoacetate obtained by the reaction of 1-octanol and cyanoacetic acid. The alkyl $–CH_2-$ stretching vibrations yielded intense peaks at 2929 and 2857 cm^{-1}. The –CN stretching occurred at 2265 cm^{-1}. The intense sharp peak at 1749 cm^{-1} is due to C=O stretch. The $–CH_2-$ bending vibrations showed peaks at 1395 and 1467 cm^{-1}. The group of peaks at 1335, 1266 and 1187 cm^{-1} is due to ester –COO- vibrations. The peak at 1007 cm^{-1} is due to –O-C vibration. The –CH2- wagging occurred at 724 cm^{-1}.

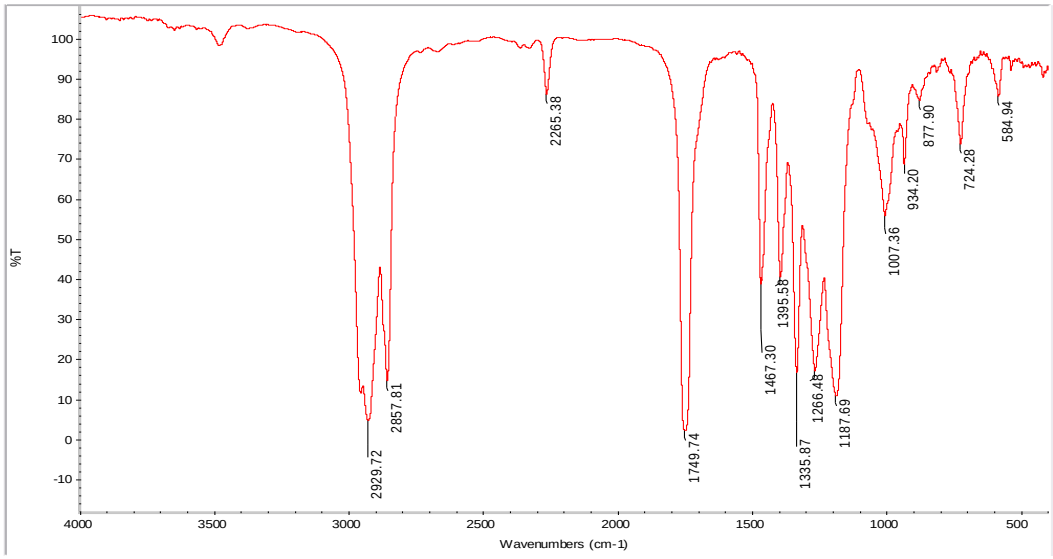

Figure 2. FTIR Spectrum of 1-Octyl Cyanoacetate

The FTIR spectrum of poly (1-octyl cyanoacrylate) obtained by the Knoevenagel condensation of 1-octyl cyanoacetate and formalin in the presence of potassium carbonate is shown in Figure 3. The intense broad peak at 3498 cm^{-1} is due to –OH stretching

vibration. It shows the product carries short chain polymers carrying –OH end groups. While the polymer obtained with piperidine is a semisolid, but the same with potassium carbonate is a highly viscous liquid. The intense broad peak at 2928 cm^{-1} is due to $–CH_2$- stretching vibration. The –CN stretching yielded a sharp peak at 2251 cm^{-1} and –C=O stretching at 1755 cm^{-1}. The $–CH_2$- bending modes occurred at 1377 and 1463 cm^{-1}. The ester –COO- vibration is very much broadened at 1241 cm^{-1}. The peak at 1060 cm^{-1} is due to –C-O- vibration. It is more intense than that of 1-octyl cyano acetate illustrating much –OH end groups. The $–CH_2$- wagging occurred at 724 cm^{-1}.

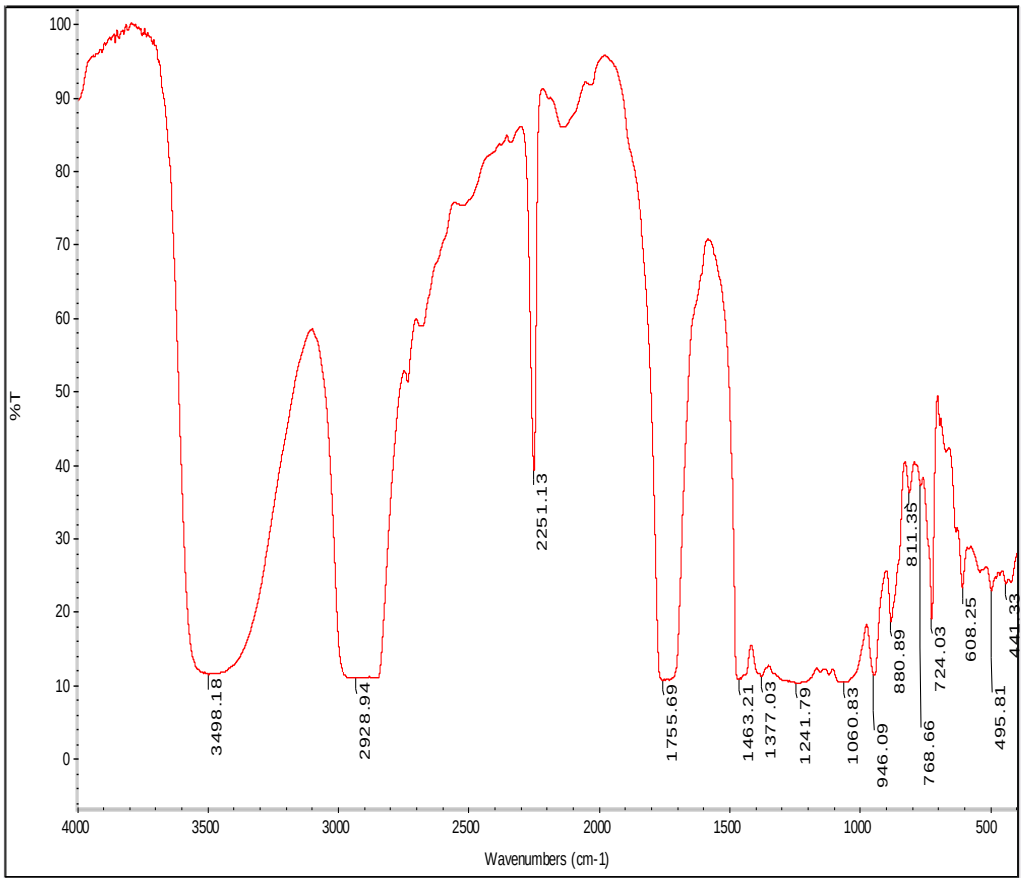

Figure 3. FTIR Spectrum of Poly (1-Octyl Cyano Acrylate)

The FTIR spectrum of 1-octyl-2-cyanoacrylate obtained by the depolymerization of the polymer mixture obtained using K_2CO_3 is shown in **Figure 4**. It indicates polymerization of the monomer, as there is an intense broad peak at 3385 cm^{-1} due to –OH stretching. T he peak at 3077 cm^{-1} and an another one close to 1620 cm^{-1} are illustrative of residual monomer. So depolymerization of the polymer is evident between 170 and 210 °C. But the process we very much tedious, as the polymerization is energy intensive.

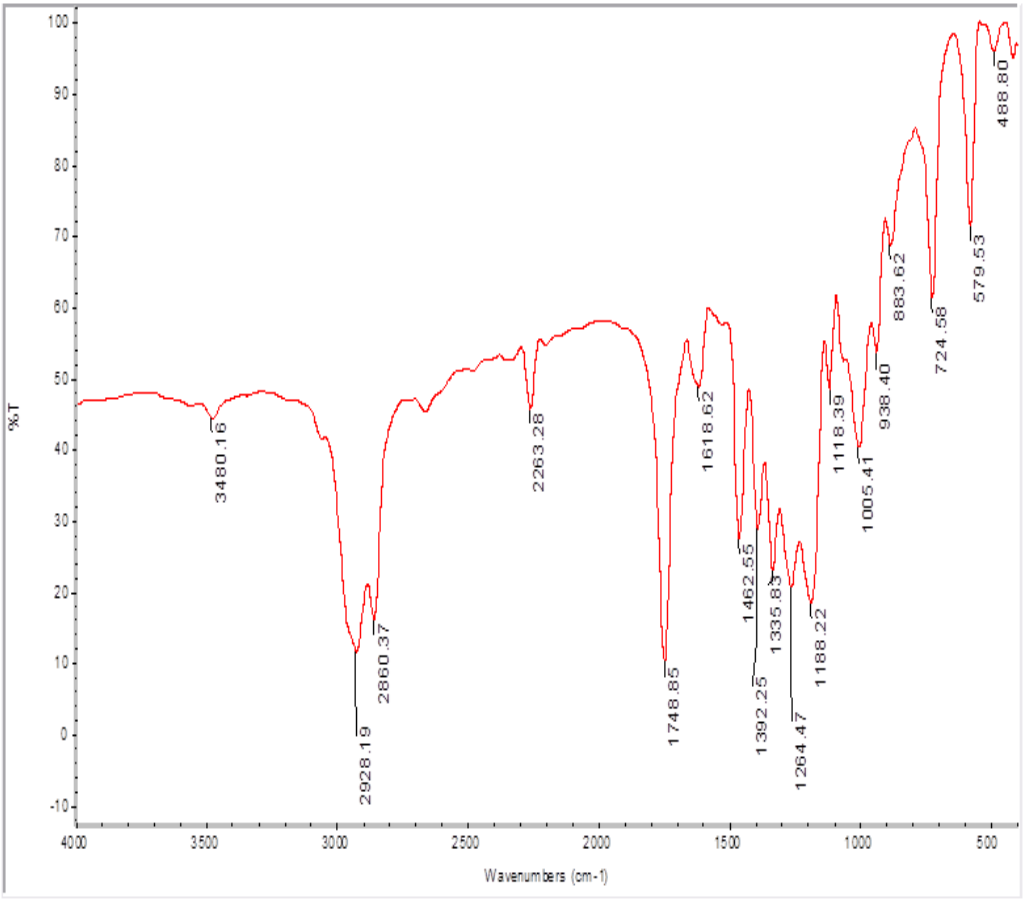

Figure 4. FTIR Spectrum of 1-Octyl-2-Cyano Acrylate

The FTIR spectrum of the polymer obtained with piperidine is shown in **Figure 5**. The broad peak at 3490 cm^{-1} is due to –OH stretching vibration of the end groups. Its intensity is lower than that of the polymer obtained with potassium carbonate supporting formation of high molecular weight polymer with piperidine and oligomers with potassium carbonate. The peaks at 2967, 2935 and 2879 cm^{-1} are due to $–CH_2$- stretching vibrations. The high energy part of this peak enters the region above 3000 cm^{-1} illustrating existence of residual unpolymerized 1-octyl cyano acrylate in the polymer matrix. It is also supported by the peak at 1612 cm^{-1} due to –C=C- stretch. It is also supported by the unsymmetrical nature of the –C=O stretching at 1l36 cm^{-1}. The –CN stretching occurred at 2250 cm^{-1}. The $–CH_2$- bending modes occurred at 1382 and 1463 cm^{-1}. The ester –COO- vibrations occurred at 1251 and 1166 cm^{-1}. The –C-O- vibration showed its peak at 1039 cm^{-1}. The - CH_2- wagging occurred at 727 cm^{-1}. So, this FTIR spectrum illustrates formation of the polymer via pre-formation of 1-octyl cyanoacrylate. The FTIR spectrum of the polymer obtained with potassium carbonate does not show any evidence for the same 1-octyl cyano acrylate; hence all the monomers might be completely polymerized, as the reaction yields only low viscous oligomers.

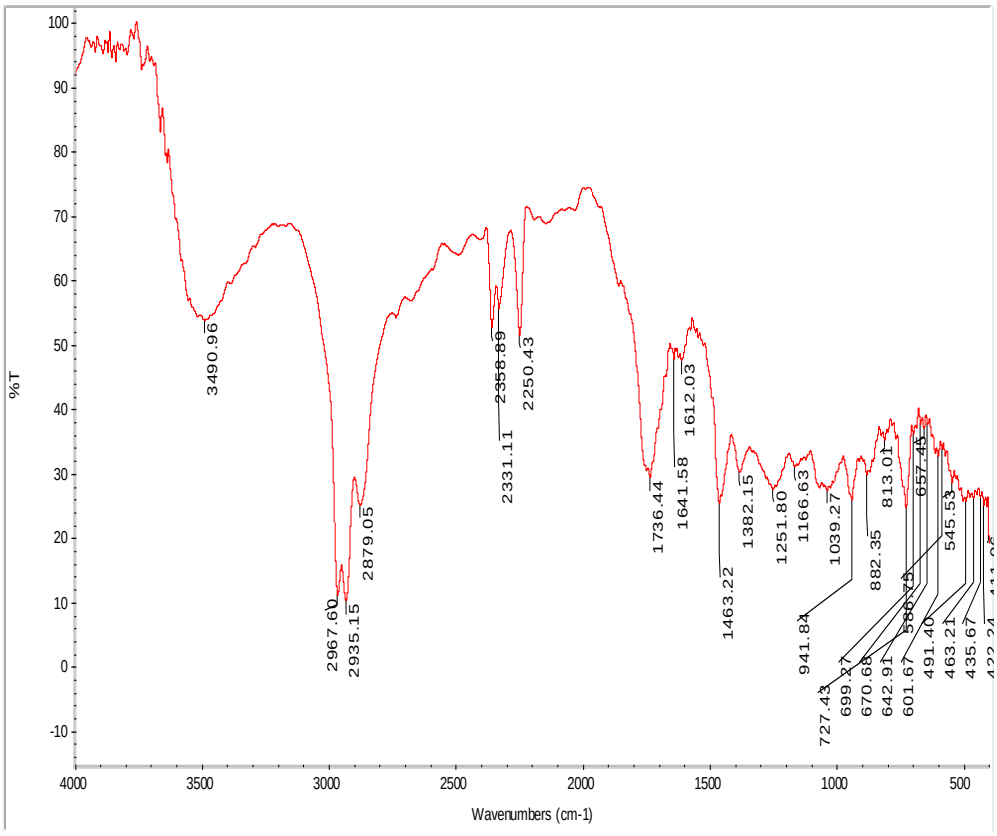

Figure 5. FTIR Spectrum of Poly (1-Octyl Cyanoacrylate) from Piperidine

The results of TGA of poly (1-octyl cyano acrylate) are illustrated in **Figure 6**. The thermogram showed absence of weight loss below 150 °C illustrating absence of any entrapped solvent. The weight loss between 150 and 225 °C is assigned to residual 1-octyl cyanoacetate. The steady weight loss between 225 and 300 °C is due to degradation of the polymer into monomer. As the decomposition occurred in one stage without leaving any residue, the decomposition evidently rejects random degradation. The polymer is proved to be formed by addition rather than condensation. The present thermogram depicts the same features as that obtained by piperidine. Hence, both the polymers are verified to be formed by addition, though their molecular weights are different. Piperidine is miscible with 1-octyl cyanoacetate; formation of 1-octyl cyanoacrylate might be more rapid than its polymerization. It accounts for formation of high molecular weight polymer with piperidine. In contrast potassium carbonate is immiscible with 1-octyl cyano acetate, so the rate of formation of polymer sight is lower than the rate of formation of 1-octyl cyano acrylate.

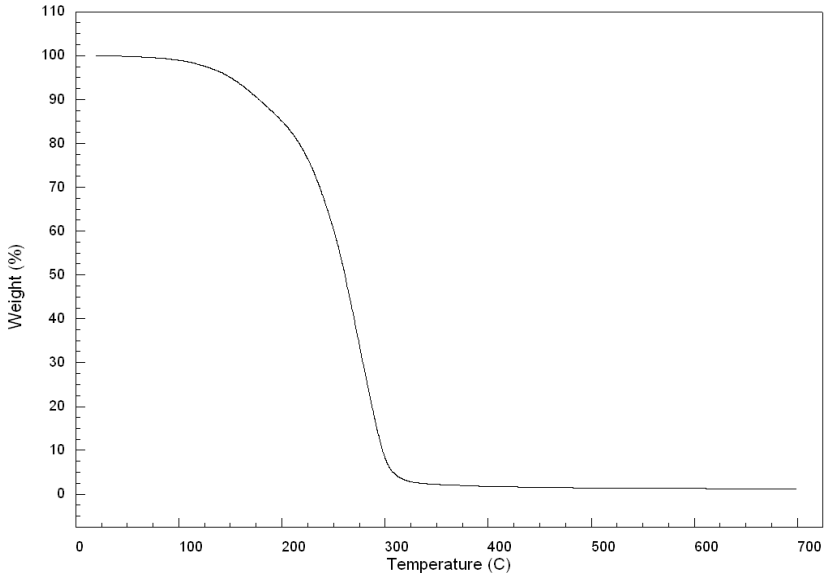

Figure 6. TGA of Poly (1-Octyl Cyano Acrylate)

The results of TGA of the polymer obtained with piperidine are shown in Figure 7. It shows similar features as that of the polymer obtained with potassium carbonate. The depolymerization temperature is slightly lowered compared to that of the polymer obtained with potassium carbonate. The elimination of water during depolymerization follows, therefore, E1 mechanism. The depolymerization occurs via protonation of the end –OH groups to form a primary carbonium ion. The stabilization of this ion by cleaving the sigma bond between the repeating units results in depolymerization to monomers. The cleavage of this bond is influenced by polymer chain length. Longer the chain, easier is to cleave that specific bond and lower the depolymerization temperature. It is the cause for the reduction of the depolymerization temperature of the long chain polymer obtained with piperidine compared to that of the oligomers obtained with potassium carbonate.

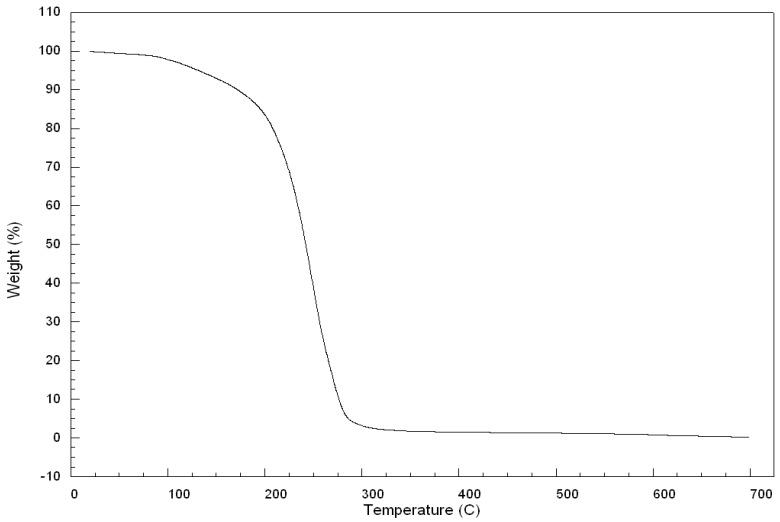

Figure 7. TGA of the Polymer Obtained with Piperidine

4. Conclusions

1- Octanol and 2-cyano acetic acid were esterified in the presence of p-toluene sulphonic acid to form 1-octyl-2-cyanoacetate. The ester was subjected to the Knoevenagel condensation with formaldehyde to form poly (1-octyl-2-cyanoacetate) using potassium carbonate or piperidine as initiators. The polymer was depolymerized using poly phosphoric acid catalyst under vacuum to obtain the monomer. A simple method of obtaining monomer was also attempted by the reaction of 1-octyl- 2-cyano acetate and diiodomethane in the presence of potassium carbonate. This process directly yields the monomer. The second method looks better than the others, and it can be applied to any type of alcohols.

Acknowledgments

This research was supported by the Korea Association of University Research Institute and Industry program funded by the Small and medium Business Administration (C0330026, 2015).

References

[1] D. M. Shivamurthy, S. Singh and S. Reddy, "Comparison of octyl-2-cyanoacrylate and conventional sutures in facial skin closure", National Journal of Maxillofacial Surgery, vol. 1, no. 1, **(2010)**, pp. 15–19.
[2] K. L. Shantha, S. Thennarasu and N. Krishnamurti, "Developments and applications of cyanoacrylate adhesives", Journal of Adhesion Sci. Tech., vol. 3, no. 4, **(1989)**, pp. 237-260.
[3] T. Gillman, J. Penn, D. Bronx and M. Roux, "A re-examination of certain aspects of the histogenesis of the healing of cutaneous wounds", Brit. Journal of Surg, vol. 43, **(1955)**, pp. 141-142.
[4] B. B. M. Nagpal, M. G. Kumar, M. G. S. Nagi and W. C. Pradeep Singh, "Sutureless closure of Operative Skin Wounds", MJAFI, vol. 60, **(2004)**, pp. 131-133
[5] A. E. Ardis, "Preparation of monomeric alkyl alpha-cyano-acrylates", US 2467926, **(1949)** April 19.
[6] H. W. Coover, F. B. Joyner, N. H. Shearer and T. H. Wicker, "Chemistry and performance of cyanoacrylate adhesives", Journal of Soc. Plast. Surg. Eng., vol. 15, **(1959)**, pp. 413-417.
[7] K. Schlueter and K. Marten, "a-Cyanoacrylic acid", DE3415181, **(1985)** October 31.
[8] S. Takahashi, Y. Ohashi, Y. Ando and T. Okuyama, "Process for producing 2-cyanoacrylic acid", US 5703267, **(1997)** December 30.
[9] K. Chen, A. S. Klapper, H. Voige and G. Del Priore, "A randomized, controlled study comparing two standardized closure methods of laproscopic port sites", Journal of Soc. Laparoendoscopic Surgeons, vol. 14, **(2010)**, pp. 391-394.
[10] A. D. Singer, G. Fananapazir, F. Maufa, S. Narra and S. Ascher, "Pulmonary embolism following 2-octyl-cyanoacrylate/lipiodol injection for obliteration of gastric varices: an imaging perspective", Journal of Radiology Case Reports, vol. 6, no. 2, **(2012)**, pp. 17-22.
[11] D. M. Ridgway, F. Mahmood, L. Moore, D. Bramley and P. J. Moore, "A blinded, randomized, controlled trial of stapled versus tissue glue closure of neck surgery incisions", Annals of the Royal College of Surgeons of England, vol. 89, **(2007)**, pp. 242-246.
[12] D. Wachter, A. Bruckel, M. Stein, M. F. Oertel, P. Christophis and D. K. Boker, "2-Octyl-cyanoacrylate for wound closure in surgical and lumbar surgery", Neurosurgical Review, vol. 33, **(2010)**, pp. 483-489.
[13] M. Mehdizadeh and J. Yang, "Design strategies and applications of tissue bioadhesives", Macromolecular Bioscience, vol. 13, no. 3, **(2013)**, pp. 271-278.
[14] R. Durai and P. CH Ng, "Easy way of gluing the skin of surgical wounds", Int. Journal of Clinical Practice, vol. 63, no. 7, **(2009)**, pp. 1115-1117.

Authors

Rajangam Vinodh, He has completed Ph.D. from Anna University, India (October 2012) with the specialization in Fuel Cells. Currently, he is working as an Assistant Professor in the Dept. of Chemical Engineering, Hanseo University, South Korea. For his credit, he has published 30 scientific papers in national and international journals.

Cadiam Mohan Babu, He has completed Ph.D. from Anna University, India (October 2014) with the specialization in water treatment. Currently, he is working as a Research Professor in the Dept. of Chemical Engineering, Hanseo University, South Korea.

Aziz Abidov, He has completed his M.S. from Hanseo University, South Korea and subsequently he registered Ph.D. in chemical Engineering with the specialization of Fluidized bed. He is actively participated many research projects under the guidance of Prof. Hyun Tae Jang.

Rramaswamy Ravikumar, He has completed M.Pharm from K.M.C.H College of Pharmacy, affiliated with The T.N. Dr. M.G.R Medical University, India (June 2009) with the specialization in Pharmaceutical Analysis. At present he is he is working as a Research Professor in the Dept. of Chemical Engineering, Hanseo University, South Korea and subsequently he registered the Ph.D in the Dept. of Chemical Engineering of the same University, under the guidance of Prof. Hyun Tae Jang.

Muthiahpillai Palanichamy, joined as a Demonstrator in the Department of Chemistry, Anna University, India in the year of 1978 and subsequently registered Ph.D. and awarded doctorate degree in 1988. For his credit, he has published more than 150 papers in reputed journals and has contributed more than 120 papers in National and International Conferences. Currently, he has been working as a visiting scientist in Prof. Hyun.-Tae Jang laboratory from 2012 onwards.

Eun Young Choi, She has completed Ph.D. from Wonkwang University, in Chemistry. Currently, she is working as an Associate Professor in the Dept. of Cosmetology, Hanseo University, South Korea from 2008. She was an Assistant Professor in the Dept. of Beauty Design, Gyeongbuk College of Health (1997-2007). Her research interests include Isolation and Whitening Effects of

Bioactive Compounds from Medicinal Plants, Morphological Changes of Human Epidermis by Cosmetics.

Hyun Tae Jang, He obtained his PhD in **1996** from the department of Chemical engineering, Korea University. He joined as a faculty member in the Department of Chemical Engineering, Hanseo University, South Korea (1997), during his research journey he has carried various research project funded by various National funding bodies. He has appointed as reviewer for various national research funding agencies. For his credit he has published more than 150 research papers in various reputed journals, presented more than 120 research articles in various conferences and more than 15 patents. His research interest include designing of sorbents for CO_2 sequestration and storage, removal of volatile organics form air and catalysis.