(Table 1). Its theoretical basis can be founded by using the genralized Boltzmann equation.

References

1. F.R. Erlich, Rheology (Academic, New York, 1967), Vol. IV., J. M.J. Hanley, Ed., Nonlinear Fluid behavior (North-Holland, Amsterdam, 1983).
2. See, for example, The Oldroyd memorial issue in J. non-Newtonian Fluid Mech. 14, January (1984).
3. R.B. Bird, O. Hassager, R.C. Armstrong and C.F. Curtiss, Dynamics of Polymeric Liquids (Wiley, New York, 1977), Vol. II.
4. W.T. Ashurst and W.G. Hoover, *Phys. Rev. A* **11,** 658 (1975).
5. J. Erpenbeck, *Phys. Rev. Lett.* **52,** 1333 (1984).
6. (a) B.C. Eu, *J. Chem. Phys.* **79,** 2315 (1983); (b) B.C. Eu and Y.G. Ohr, *J. Chem. Phys.* **81,** 2756 (1984).
7. S. Hess, Phys. Lett. **A90,** 293 (1982).
8. B.C. Eu, *Ann. Phys.* (N.Y.) **140,** 341 (1982).
9. B.C. Eu, *Ann. Phys.* (N.Y.) **118,** 187 (1979).
10. B.C. Eu, *J. Chem. Phys.* **73,** 2958 (1980).
11. N. Minorski, Nonlinear Oscillations (R.E. Krieger, Malbar, Florida, 1983).
12. G. Kiss and R.S. Porter, *J. Polymer Sci.: Polymer Phys. Ed.* **18,** 361 (1980).
13. K.F. Wissbrun, *J. Rheol.* **25,** 619 (1981); S.G. Mason, *J. Rheol.* **26,** 399 (1982).
14. A.C. Eringen, Mechanics of Continua (Wiley, New York, 1967).
15. B.C. Eu, *J. Chem. Phys.* **82,** 3773 (1985).
16. W. Prager, Introduction to Mechanics of Continua (Ginn, Boston, 1961).
17. R.F. Gantmacher, Theorie des Matices (Dunod, Paris, 1966), Vol. 2.
18. E.F. Beckenbach and R. Bellman, Inequalities (Springer, Berlin, 1961).
19. J.D. Huppler, E. Ashare and L.A. Holmes, *Trans. Soc. Rheol,* **11,** 159 (1967).
20. E.B. Christiansen and W.R. Leppard, *Trans. Soc. Rheol.* **18,** 65 (1974).
21. M. Keentok and R.I. Tanner, *J. Rheol.* **26,** 301 (1982).

Synthesis and Ring-Opening Polymerization of 1,2-Disubstituted Cyclobutanes

Ju-Yeon Lee*

Department of Chemistry, Inje College, Aebang-Dong, Kimhae 600-60

Iwhan Cho

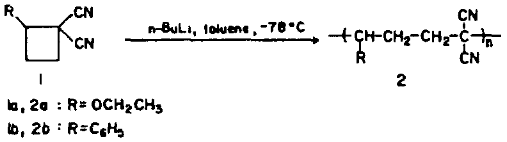
Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131

Received February 24, 1986

1,1-Dicyano-2-ethoxycyclobutane (**1a**) was prepared by [2+2] cycloaddition reaction of vinylidene cyanide with ethyl vinyl ether. 1,1-Dicyano-2-phenylcyclobutane (**1b**) was prepared by the reactions involving the reduction of cinnamyl alcohol, chlorination, cyanomethylation, bromination, and ring-closure reaction. Compound **1a** was ring-opening polymerized with NaCN or n-butyllithium to give a low molecular weight polymer. The compound **1b** however, failed to polymerize by either anionic or radical catalysts.

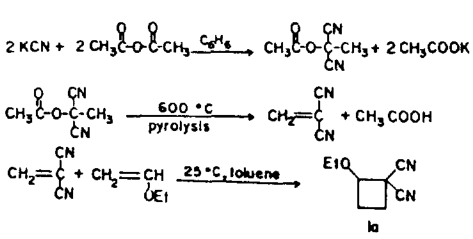
Introduction

Previously we have reported ring-opening polymerization of various substituted cyclopropanes[1-4] with radical or anionic initiators. These substituted cyclopropanes have various radical- or anion-stabilizing groups at the proper position of the cyclopropane ring. This substituent effect was also demonstrated in the ring-opening polymerization of 2-methylene-4-phenyl-1,3-dioxolane[5] and 2-phenyl-3-vinyloxirane.[6] We have extended this concept to the substituted cycobutanes and the present report describes the synthesis and ring-opening polymerization of 1,1-dicyano-2-ethoxycyclobutane (**1a**) and 1,1-dicyano-2-phenylcyclobutane (**1b**).

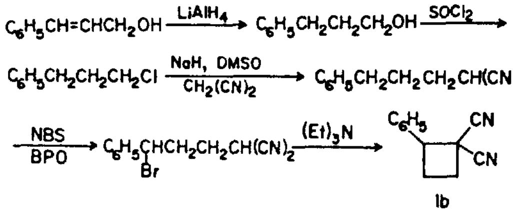


Results and Discussion

Monomer **1a** was prepared[7] as shown in Scheme I, by reacting ethyl vinyl ether and vinylidene cyanide. Vinylidene cyanide.[8] Monomer **1b** was synthesized by the reactions involving the reduction of cinnamyl alcohol, chlorination, cyanomethylation, bromination, and ring-closure reaction, as shown in Scheme II.



Scheme I



Scheme II

The chemical structures of the reaction products were confirmed by ^{1}H NMR (Figure 1 and 2) and IR spectra (Figure 3). All the spectral data confirmed the expected structures.

Polymerizations were carried out either in DMSO solution with NaCN at 25°C, or in toluene solution with n-butyllithium at −78°C. Radical polymerizations were also attempted. Monomer **1a** was polymerized with NaCN or n-butyllithium to give a low molecular weight polymer. Thus obtained polymer **2a** was soluble in common solvents and were reprecipitated by pouring its acetone solution into methanol. The results are summarized in Table 1. The values in Table 1 shows that **1a** is not as reactive as some of the 1,1-disubstituted cyclopropanes which we have reported previously,[3] failing to give high molecular weight polymers. Both monomers **1a** and **1b** were inert to radical initiators and all the attemps to polymerize **1b** with various initiators failed.

The chemical structures of the polymers were determined by IR (Figure 4) and ^{1}H NMR spectra (Figure 5). The ^{1}H NMR spectrum of polymer **2a** shows resonance peaks attributable to methyl protons at $\delta = 0.9-1.3$ (3H, $-CH_3$). The signals of methylene protons of backbone chains are observed at $\delta = 1.8-2.4$ (4H, $-CH_2-CH_2-$). The same polymer sample showed strong absorption band at 2220 cm^{-1} indicating the presence of nitrile groups as shown in Figure 4. These spectral evidence indicates that the polymerization proceeded via a ring-opening fashion by the cleavage of 1,2-bond of the butane ring.

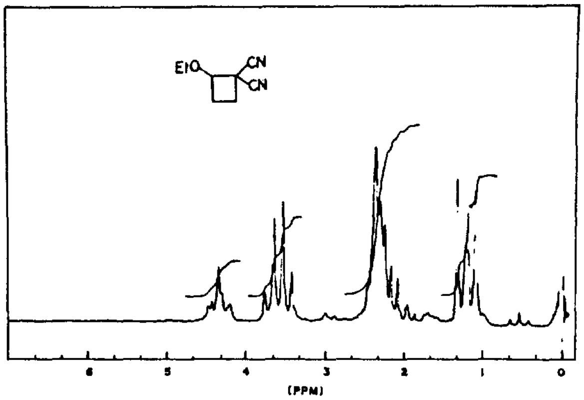
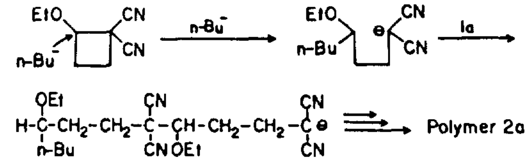


Figure 1. 60 MHz ^{1}H NMR spectrum of 1,1-dicyano-2-ethoxycyclobutane (**1a**) taken in $CDCl_3$ at room temperature.

As in the case of 1,1-disubstituted cyclopropanes such as 2-phenylcyclopropane-1,1-dicarbonitrile,[3] the anionic ring-opening polymerization behavior of substituted cyclobutanes also seems to be attributable to their electronic character. In the presently investigated carbocyclic monomer systems substitutents of electron-donating and electron-withdrawing properties are positioned such a way that an electronic "push-pull" system is achieved, activating the 1,2-bond by zwitterionic polarization. The substituent at position 1 has electron-withdrawing character, thus having the capability of stabilizing the propagating anion. In the polymerization reaction the catalyst initiates the polymerization by attacking a monomer molecule at C_2 thereby resulting in the formation of an anion, which is usually involved in the anionic polymerization of vinylidene cyanide.



The striking feature of the ring-opening polymerization of substituted cyclobutanes is that it provides a synthetic route to H-H alternating copolymer systems as in the case of 3,4-dihydro-2H-pyrans.[9] According to our experience[10] the cyclopropane moiety similar to **1a** is too reactive to isolate in a monomer form. However, contrary to our expectation, the substituents employed in the present monomer systems did not activate enough the cyclobutane ring for the successful polymerizations.

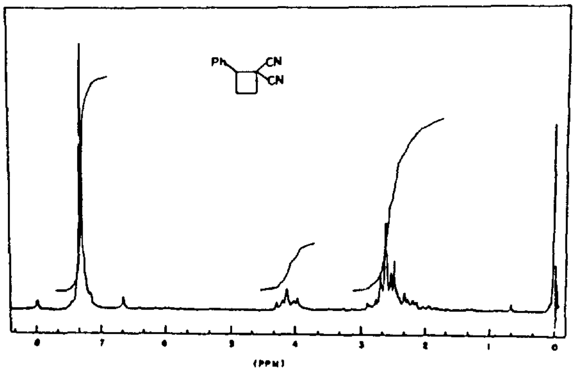


Figure 2. 60 MHz ^{1}H NMR spectrum of 1,1-dicyano-2-phenylcyclobutane (**1b**) taken in $CDCl_3$ at room temperature.

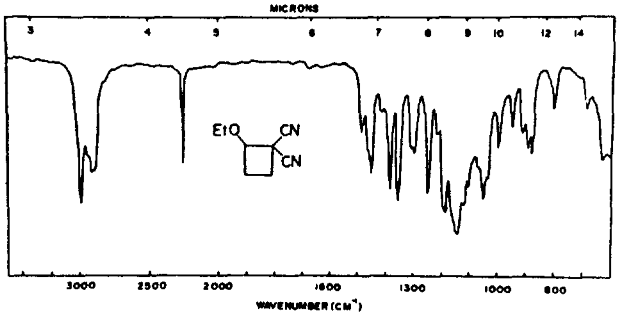


Figure 3. IR spectrum of 1,1-dicyano-2-ethoxycyclobutane (**1a**).

Table 1. Ring-Opening Polymerization of 1,1-Dicyano-2-Ethoxycyclobutane under Various Condition

Monomer	Initiator		Wt. of monomer/ vol. of solvent (g/ml)	Temp. (°C)	Time (hr)	Conversion (%)	η_{inh} (dl/g)
	Type	Conc. (mol %)					
1a	AIBN	0.8	neat	60	10	nil	
1a	NaCN	1.8	DMSO, 0.38	25	72	32	0.03[a]
1a	NaCN	2.0	DMSO, 0.25	25	144	36	0.04[a]
1a	n-BuLi	2.2	neat	-30	48	74	0.06[b]
1a	n-BuLi	2.5	toluene, 0.20	-78	25	72	0.06[b]
1a	n-BuLi	2.4	toluene, 0.20	-78	36	73	0.08[b]

[a] Concentration of 1.0 g/dl in acetone at 25°C. [b] Concentration of 0.5 g/dl in DMSO at 25°C.

We are exploring further the present polymerization system including the substituted vinylcyclobutanes and the full accounts of the work will be published later.

Experimental

1-Acetoxy-1,1-dicyanoethane. 1-Acetoxy-1,1-dicyanoethane was prepared by a known method[8] from acetic anhydride and potassium cyanide. 24.7g (55% yield): bp 85-90°C/5mmHg (lit.[8] 100-110°C/10mmHg): ^{1}H NMR($CDCl_3$) δ 2.10 (*s*,3H), 2.20 (*s*,3H); IR (KBr) 2230 (C≡N), 1760 (C=O) cm^{-1}.

Vinylidene cyanide. Vinylidene cyanide was prepared according to a procedure similar to that reported already[8] and recrystallized from chloroform, followed by fractional distillation. 10.0g (33% yield): bp 49-51°C/10mmHg: ^{1}H NMR($CDCl_3$) δ 6.65 (*s*,2H).

1,1-dicyano-2-ethoxycyclobutane (1a). Monomer **1a** was prepared according to a procedure similar to that reportred already[7] in a toluene solvent at 25°C. 6.3g (25% yield): bp 55-57°C/0.2mmHg: ^{1}H NMR($CDCl_3$) δ 1.05-1.40 (*t*,3H), 1.90-2.50 (*m*,4H), 3.40-3.75 (*q*,2H): IR(neat) 2240 (C≡N) cm^{-1}.

3-Phenyl-1-propanol. Cinnamyl alcohol (55.0g, 0.41 mol) dissolved in 150 m*l* of diethyl ether was added to 160 m*l* of an ether solution containing, 9.45g (0.25 mol) of $LiAlH_4$. The white precipitated which was formed after half of the alcohol was added was redissolved after heating the mixture under reflux for two hours. Then 50 m*l* of water was added to the clear solution, resulting in the evolution of H_2 gas. Dilute H_2SO_4 (30m*l*) was added and ether layer was separated. After evaporation of solvent the resulting viscous liquid was distilled. 51.3g (92% yield): bp 95-97°C/0.4mmHg: ^{1}H NMR (neat) δ 1.15-1.65 (*q*,2H), 2.05-2.35 (*t*,2H), 2.95-3.27 (*s*,2H), 4.45 (*s*,1H), 6.65 (*s*,5H): IR (neat) 3650-3150 (O-H) cm^{-1}.

1-Chloro-3-Phenylpropane. Thionyl chloride (89g) was placed in the 250 m*l* round-bottomed flask and fitted Claisen connecting tube to the flask. A reflux condenser was fitted into the Claisen tube and to the top of the condenser was attached a tube connected to an inverted funnel dipping just below the surface of 200 m*l* of aqueous NaOH solution. Then 3-phenyl-1-propanol was added through a dropping funnel during two hours. When all the alcohol was added, the reaction mixture was refluxed for two hours. The apparatus was rearranged for distillation and the excess thionyl chloride was distilled off slowly. The final fraction was washed successively with water, 10% K_2CO_3 solution, and water. After drying over anhydrous $CaCl_2$, the resulting liquid was distilled under vacuum, 35.5g (93% yield): bp 86-88°C/0.3mmHg: ^{1}H NMR ($CDCl_3$) δ 1.93-2.30 (*q*,2H), 2.62-2.97 (*t*,2H), 3.32-3.60 (*t*,2H), 7.18 (*s*,5H).

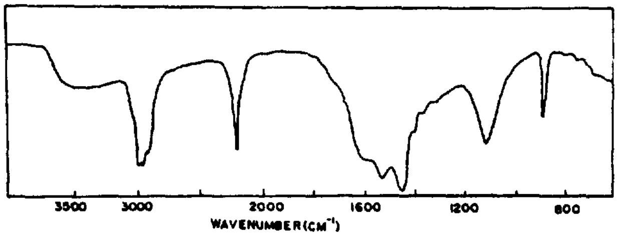


Figure 4. IR spectrum of poly(1,1-dicyano-2-ethoxycyclobutane) (**2a**).

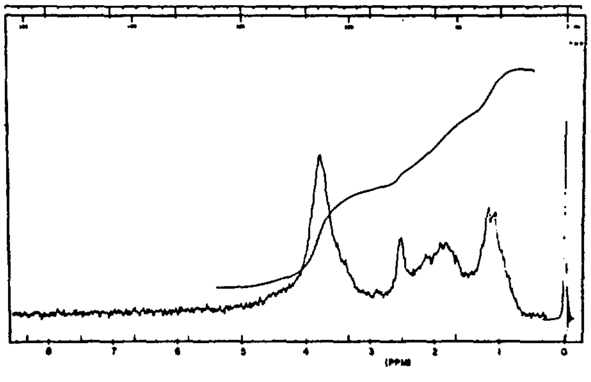


Figure 5. 60 MHz ^{1}H NMR spectrum of poly(1,1-dicyano-2-ethoxycyclobutane) (**2a**).

1,1-Dicyano-4-phenylbutane. DMSO (75m*l*) solution of NaH (12.0g, 0.5 mol) was added to the solution of malononitrile (16.5g, 0.25 mol) dissolved in DMSO (45 m*l*) during 20 minutes. The mixture was stirred for a further 20 minutes with cooling (0°C), then 1-chloro-3-phenylpropane (77.2g, 0.5 mol) was added during 25 minutes with cooling. Then whole mixture was stirred for 9 hours at room temperature and then was poured into 100 m*l* of cold water. The organic layer was distilled under vacuum. 13.8g (15% yield): bp 95-98°C/0.1mmHg: ^{1}H NMR($CDCl_3$) δ 1.95-2.15 (*m*,4H), 2.65-2.90 (*m*,2H), 3.55-3.80 (*m*,1H), 7.25 (*s*,5H); IR (neat) 2250 (C≡N) cm^{-1}.

1,1-Dicyano-4-bromo-4-phenylbutane. N-Bromosuccinimide (8.9g, 0.05 mol), benzoyl peroxide (1.0g), 1,1-dicyano-4-phenylbutane (18.4g, 0.1 mol), and dry CCl_4 (20 m*l*) were placed in a 100 m*l* round-bottomed flask. The mixture was refluxed for 12 hours. After filtering off the succinimide the solvent was removed by rotary evaporator. The resulting viscous liquid was placed in a refrigerator (−30°C) to crystallize. White crystal was collected and recrystallized from ethanol. 5.9g (45% yield): ^{1}H NMR($CDCl_3$) δ 1.08–2.70 (*m*,4H), 3.70 (*t*,1H), 4.98 (*t*,1H), 7.35 (*s*,5H): IR (KBr) 2260 (C≡N) cm^{-1}.

1,1-Dicyano-2-phenylcyclobutane (1b). In a 250 m*l* round-bottomed (3-neck) flask fitted with a reflux condenser and a dropping funnel containing a dry benzene (10 m*l*) solution of triethylamine (12.0g, 0.12 mol) was placed a benzene (40 m*l*) solution of 1,1-dicyano-4-bromo-4-phenylbutane (26.3g, 0.1 mol). The reaction mixture was heated to reflux with stirring and the amine solution was added slowly during two hours. The reflux was continued for an additional three hours. The brown precipitate was removed by filtration. The resulting liquid was distilled under reduced pressure. 4.0g (22% yield): bp 50–52°C/0.1mmHg: ^{1}H NMR($CDCl_3$) δ 2.05–2.95 (*m*,4H), 3.85–4.35 (*m*,1H), 7.30 (*s*,5H): IR (neat) 2240 (C≡N) cm^{-1}.

Anionic polymerization of 1. A represent anionic polymerization procedure were as follows: In a rubber stopper-capped glass ampoule were placed a solution of **1a** (1.5g, 0.01 mol) and 4 m*l* DMSO. Dry N_2 gas was passed through the solution by a syringe needle for 30 minutes. The solution was then cooled in a dry ice-acetone bath and it was added proper quantities of initiator solution by a microsyringe. The ampoule was then evacuated and sealed under vacuum. The sealed ampoule was taken out of dry ice-acetone and allowed to stand at room temperature. As polymerization proceeded, red color developed and viscosity of the solution increased. After three days the ampoule was opened and the polymer solution was poured into a large volume of cold methanol. Precipitated polymer was collected and reprecipitated from acetone into methanol. Thus obtained polymer was then dried in a vacuum oven at room temperature. 0.54g (36% yield); $\eta_{inh} = 0.03$ dl/g (c: 1.0 g/dl in acetone at 25°C).

Measurements. IR spectra were taken on a Perkin-Elmer Model 283B spectrophotometer. ^{1}H NMR spectra were obtained with a Varian Model T-60A spectrometer (60 MHz) at room temperature.

Acknowledgement. This work was financially supported by Ministry of Education in Korea.

References

1. I. Cho and K.D. Ahn, *J. Polym. Sci., Polym. Chem. Ed.*, **17**, 3169 (1979).
2. I. Cho and K.D. Ahn, *J. Polym. Sci., Polym. Chem. Ed.*, **17**, 3183 (1979).
3. I. Cho and J.B. Kim, *J. Polym. Sci., Polym. Chem. Ed.*, **18**, 3053 (1980).
4. I. Cho and J.Y. Lee, *Makromol. Chem., Rapid Commun.*, **5**, 263 (1984).
5. I. Cho and M.S. Gong, *J. Polym. Polym. Lett. Ed.*, **20**, 361 (1982).
6. I. Cho and J.B. Kim, *J. Polym. Sci., Polym. Lett. Ed.*, **21**, 433 (1983).
7. J.K. Stille and D.C. Chung, *Macromolecules*, **8**, 114 (1975).
8. S. Kleeman, *Ber.*, **18**, 256 (1885).
9. I. Cho and J.Y. Lee, *Macromolecules*, **16**, 1245 (1983).
10. J.B. Kim, "Anionic Polymerization of 2-Substituted Cyclopropane-1,1-dicarbonitriles" M.S. Thesis, KAIST (1980).

Preparation of Glutamic Acid-Leucine Copolymer Containing Indomethacin for Controlled Delivery

Young Il Yeom, Hyun-Pyo Kim, Hack-Joo Kim, and Si Myung Byun*

Department of Biological Science & Engineering, The Korea Advanced Institute of Science & Technology, Seoul 131

Nam Deuk Kim

College of Pharmacy, Pusan National University, Pusan 605. Received February 25, 1986

A series of copolypeptides of glutamic acid and leucine have been synthesized by N-carboxy-α-amino acid anhydride procedure and cast to form injectable microparticulate monolithic devices in which indomethacin was physically dispersed. With these devices, various release properties and possible clinical application were studied. The release rate of the drug had a close relationship with the monomer composition of the copolymer matrix as well as the environmental pH condition. The monolithic device of glutamic acid/ leucine = 50/50 was found to be the most promising one as a ploymeric delivery system of indomethacin. The intrinsic viscosity of this copolymer was 4.35 dl/g and the release rate was 18.5 μg/g/day.

Introduction

Among the many types of drug delivery systems, controlled delivery using wide varieties of polymers and drug entrapping method is one of the most efficient ways to deliver the drug to a specific body site over a desired time period.[1-3] Compared to the other polymeric delivery systems, those of the biodegradable polymers have a unique property in that the polymer matrices are degraded to nontoxic products in the body during or after the release of drugs so that they are