

## Synthesis and Degradation of Poly(alkyl $\alpha$ -Cyanoacrylates)

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### Synopsis

In order to study structure-tissue reactivity relationships and ultimately develop a less necrotizing adhesive, this laboratory undertook a study of the synthesis and degradation of the homologous series of  $\alpha$ -cyanoacrylate monomers and polymers. A method for synthesizing high purity cyanoacrylates and some of their chemical and physical properties are presented. *In vitro* kinetics studies under heterogeneous and homogeneous conditions indicate that cyanoacrylate polymers degrade by hydrolytic scission of the polymer chain. The products resulting from such a scission are formaldehyde (positively identified by derivative formation) and ultimately an alkyl cyanoacetate. As the homologous series is ascended, the rate of degradation under neutral conditions decreases. In homogeneous solution, under alkaline conditions, the rate of degradation is considerably higher than under neutral conditions and the rates obtained with the methyl to the butyl derivative are of the same order. A proposed mechanism of degradation is presented. Medical evaluation has indicated that as the homologous series is ascended, the greater the tissue tolerance to the monomers and polymers. The relevance of the results of the *in vitro* studies to this medical finding is presented.

The capability of rapidly polymerizing monomeric  $\alpha$ -cyanoacrylates to adhere firmly to moist surfaces has evoked considerable medical interest in their potentialities as hemostatic agents and tissue adhesives for closure of wounds in place of, or as adjuncts to, the conventional surgical sutures.<sup>1</sup> Evaluation of methyl  $\alpha$ -cyanoacrylate in such applications revealed that tissue inflammation and cell necrosis occurred in experimental animals.<sup>2,3</sup> Research in this laboratory further showed that the  $\beta$ -<sup>14</sup>C-tagged methyl  $\alpha$ -cyanoacrylate polymer was degraded gradually *in vivo*<sup>4</sup> and was excreted in the urine and feces with none of the radioactive entities being retained in vital tissues or organs. Concomitantly, it was discovered<sup>4</sup> that the polymer of methyl  $\alpha$ -cyanoacrylate underwent degradation in contact with distilled water *in vitro*, giving rise to formaldehyde, analogous to the degradation of poly(vinylidene cyanide), reported by Gilbert and co-workers.<sup>5</sup>

In order to elucidate structure-tissue reactivity relationships and ultimately develop a less necrotizing adhesive, this laboratory undertook the

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synthesis and evaluation of the homologous series of the alkyl  $\alpha$ -cyanoacrylates. It was postulated that the higher homologs might degrade at a slower rate, thereby permitting the degradation products to be more safely metabolized with the evocation of a lesser inflammatory response.

In this paper we report on a convenient technique of synthesizing the homologous series of monomers, their physical properties with respect to purity, and also the kinetics of *in vitro* degradation of poly(alkyl  $\alpha$ -cyanoacrylates) in the presence of water, both in the heterogeneous and homogeneous phases. Other important findings on the mode of polymerization are given, and comparisons of *in vitro* with the *in vivo* degradation results are made.

## EXPERIMENTAL

### Preparation of Monomers

The method described below for butyl  $\alpha$ -cyanoacrylate is generally applicable to monomers ranging from methyl to decyl based on modification of the work of Jeremias.<sup>6</sup> The procedure adopted was as follows.

**Butyl- $\alpha$ -Cyanoacrylate.** Paraformaldehyde (135 g.), 300 ml. of methanol, 100 ml. of diglyme (dimethyl ether of ethylene glycol), 2.0 ml. of piperidine, were placed in a two-liter three-necked flask, fitted with a mechanical stirrer, water-cooled condenser, Dean and Stark trap, and dropping funnel.

This mixture was stirred and heated until the methanol refluxed vigorously. Then a 5-mole portion of butyl cyanoacetate (705 g.) was added through a dropping funnel at a rate sufficient to maintain reflux, after removal of the external heat source. After the addition, methanol was distilled off until the vapor temperature reached 88°C. Benzene (250 ml.) was added, and water was removed from the reaction mixture by azeotropic distillation. The apparatus was converted to a conventional distillation set up, and a total of 3.5 mole water was removed. An essential characteristic of the setup was the short path through the condenser providing a small glass area in contact with the monomer vapors. At this stage, 15 g. of phosphorus pentoxide was added, benzene was removed under water aspirator, and residual benzene and diglyme were removed at 3 mm. Hg. The vacuum distillation was continued until the pot temperature reached 160°C. to remove any residual unreacted butyl cyanoacetate. At this point, cracking began to occur, and a receiver with small amounts of pyrogallol and phosphorus pentoxide was attached to the apparatus, and the monomer was collected. Some polymer may tend to form at this stage on the sides of the distilling adaptors; however, the replacement of the adaptors and addition of another charge of 15 g. of phosphorus pentoxide to the reaction mixture minimizes this condition. Over 500 g. of crude monomer collected was redistilled through a 6-in. Vigreux column. A sulfur dioxide bleed was introduced through a capillary tube as an inhibitor to prevent anionic polymerization and also bumping during distillation.

The monomers obtained after redistillation were found to have average purities of 98.5% and better, based on the peak areas on the gas chromatograms. In many instances the purities were 99% or higher.

**Gas Chromatography.** The gas chromatograms on the monomer samples were run on a Model F & M 700 chromatograph, with a silicone gum nitrile column (6 ft.) with Diatoport as solid support, in dual column operation at column temperatures of 150°C. and 170°C. The monomers were dissolved in spectrograde nitromethane or methylene chloride, to make 10% solutions prior to injection in the columns to obviate the difficulties of clogging the injection syringe and needle experienced when pure monomers were used. The detailed results of the chromatographic study will be published elsewhere.

Refractive indices were determined by using a Bausch & Lomb dipping refractometer at 20°C. with sodium light. Densities and surface tensions were determined on a Westphal balance and du Nouy tensiometer, respectively, both at 20°C. The molecular constants, parachor, and molar refraction were calculated.

### Preparation of Polymer Samples

The poly(alkyl  $\alpha$ -cyanoacrylates) used for the study of degradation kinetics were prepared by polymerizing the respective monomer samples by anionic initiation with methanol. Later the polymers formed were precipitated in the powder form by diluting with water and small amounts of sodium chloride. The samples were thoroughly washed with water and methanol and dried under high vacuum at 40°C. to constant weight.

### Degradation in Heterogeneous Phase

Poly  $\alpha$ -cyanoacrylates degrade slowly in the presence of distilled water, producing formaldehyde as one of the products. The following general technique was used to study this degradation.

Cyanoacrylate polymer (1 g.) was placed in a Soxhlet thimble and extracted with 100 ml. of water for 4 hr. This treatment solubilizes a portion of the polymer. The water was then distilled away and the procedure was repeated with fresh water, and the quantities of formaldehyde determined on each run were plotted cumulatively against time of extraction. The amount of formaldehyde contained in the samples was estimated by the method of Bricker and Johnson,<sup>7</sup> in which formaldehyde was allowed to react with 1,8-dihydroxy-3,6-disulfonic acid (chromotropic acid) in presence of sulfuric acid. The color developed was determined by measuring the absorption at 570  $m\mu$  on a Beckman spectrophotometer. The method is as follows.

A 0.5-ml. sample was placed in a 100-ml. Kjeldahl digestion flask, along with 0.5 ml. of 10% chromotropic acid reagent in water. Concentrated sulfuric acid (5 ml.) was added with continuous shaking. After digesting the reaction mixture on a boiling water bath for  $\frac{1}{2}$  hr., the flask was cooled, the mixture was diluted with 30 ml. of cold water and made to 50

ml. in a volumetric flask. The absorbency of the solution was determined on a Beckman DK-2A spectrophotometer. The concentration of formaldehyde was estimated from an accurately determined calibration curve of absorbency against known solutions of formaldehyde. The method was found to be accurate in estimation of formaldehyde down to 2–3 ppm.

### Degradation in Homogeneous Phase

After preliminary investigation, aqueous acetonitrile was selected as the medium for use in the study of homogeneous degradation of these polymers. Although other systems, like dioxane–water or dimethylformamide–water, could be used, these solvents interfered with the technique of determination of formaldehyde by the method of Bricker and Johnson.<sup>7</sup> The general method followed for the various polymers is as follows. The polymer (0.02 basal mole) was dissolved in 100 ml. of aqueous acetonitrile containing 5.04 ml. of water (0.28 mole) and refluxed under a water-cooled condenser. Aliquots (10 ml.) were pipetted out at definite intervals and treated with 100 ml. of saturated salt solution. The precipitated polymer was filtered through a sintered glass funnel, and the filtrate was distilled. The aliquots (0.5 ml.) from the distillate were subjected to formaldehyde estimation in each case. The amount of formaldehyde obtained per mole of polymer was calculated.

### Identification of Formaldehyde

That formaldehyde was produced by the hydrolytic degradation of polycyanoacrylates was proven by the preparation of two derivatives of the 2,4-dinitrophenylhydrazine and dimethylcyclohexanedione (methone). The melting points of the derivatives made from the unknown, of derivatives of a known formaldehyde sample, and mixed melting points were determined. (Table I).

TABLE I  
Proof of Presence of Formaldehyde

Derivative	M.P. known formaldehyde sample, °C.	M.P. unknown sample, °C.	Mixed melting point, °C.	M.P. (lit.) formalde- hyde, °C.	M.P. acetal- dehyde (lit.), °C.
2,4-Dinitrophenyl- hydrazone	164–165	160–161	163–164	166–167	168.5
Methylene bisdime- done	190	191	190.5	191.4	140

### Average Molecular Weights

The number-average molecular weights were determined in acetonitrile by using the Mechrolab 301A vapor phase osmometer.

## RESULTS AND DISCUSSION

## Synthesis of Monomers

Although details of preparative procedures for the synthesis of monomers is available in patent literature,<sup>8,9</sup> in our experience, it was found necessary to modify the procedures to obtain high purity products. The pyrogallol and tricresyl phosphate used in the cracking stage were found to introduce pyrolytic impurities in the distilling monomers, necessitating further fractional distillation. However, when these two ingredients were eliminated and diglyme was used as a diluent, pure monomers could be obtained in a single redistillation.

The parachor and molar refraction determined on the monomer samples prepared showed a high degree of consistency within the homologous series and compared favorably with the calculated values obtained from the theoretical constants for the individual atoms, groups and bonds already established. These data are summarized in Table II and in Figures 1 and 2. The close agreement between calculated and theoretical values along with the data on purity obtained through the use of gas chromatography are further indications of the purity of the monomers.

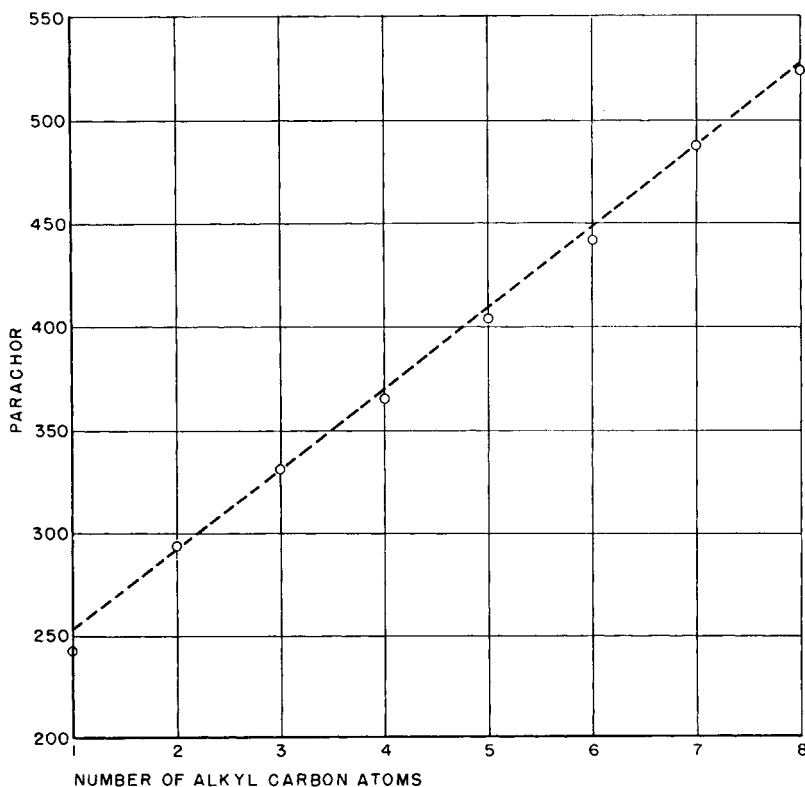


Fig. 1. Parachor values of alkyl cyanoacrylates: (O) found; (--) theoretical.

TABLE II  
 Physical Properties of Cyanoacrylate Esters

Cyano- acrylate ester	Molecular weight	Boiling point, °C./ mm. Hg.	Density (20°C.), g./cc.	Index of refraction (20°C.)	Surface tension, dynes/cm.
Methyl	111	55/4	1.1044	1.4459	37.41
Ethyl	125	60/3	1.040	1.4391	34.32
Propyl	139	80/6	1.001	1.4408	32.80
Butyl	153	68/1.8	0.989	1.4424	31.11
Amyl	167	113/5.4	0.972	1.4440	30.25
Hexyl	181	90/1.6	0.958	1.4458	29.98
Heptyl	195	125/1.2	0.942	1.4466	30.28
Octyl	209	117/1.8	0.931	1.4489	29.18
Allyl	137	74/4.2	1.066	1.4586	35.38

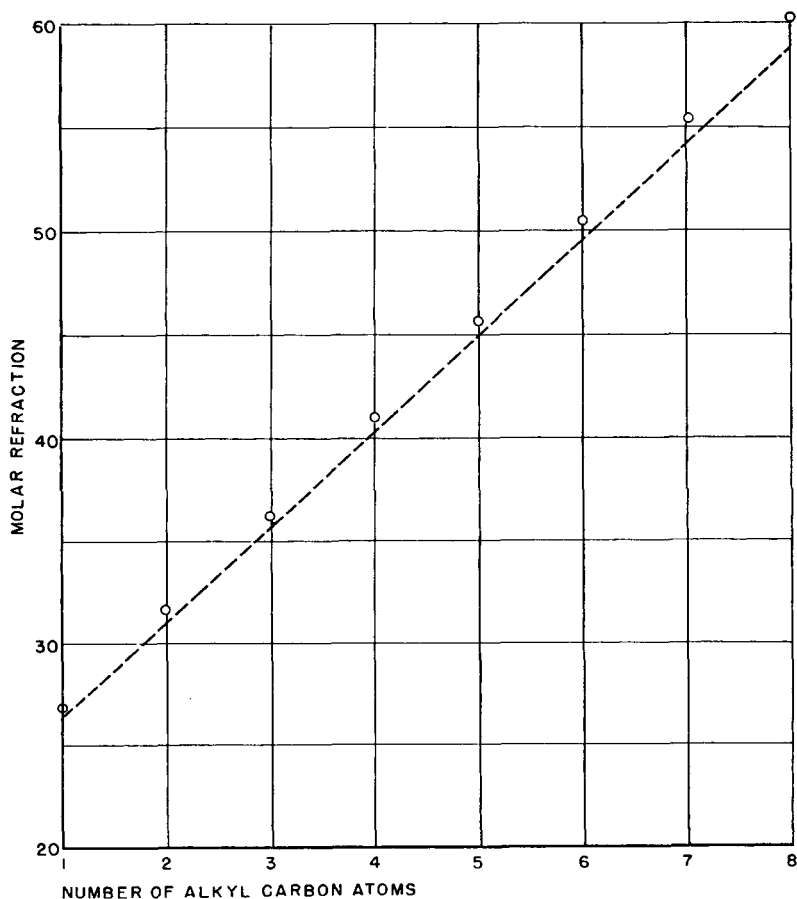


Fig. 2. Molar refraction of alkyl cyanoacrylates: (O) found; (—) theoretical.

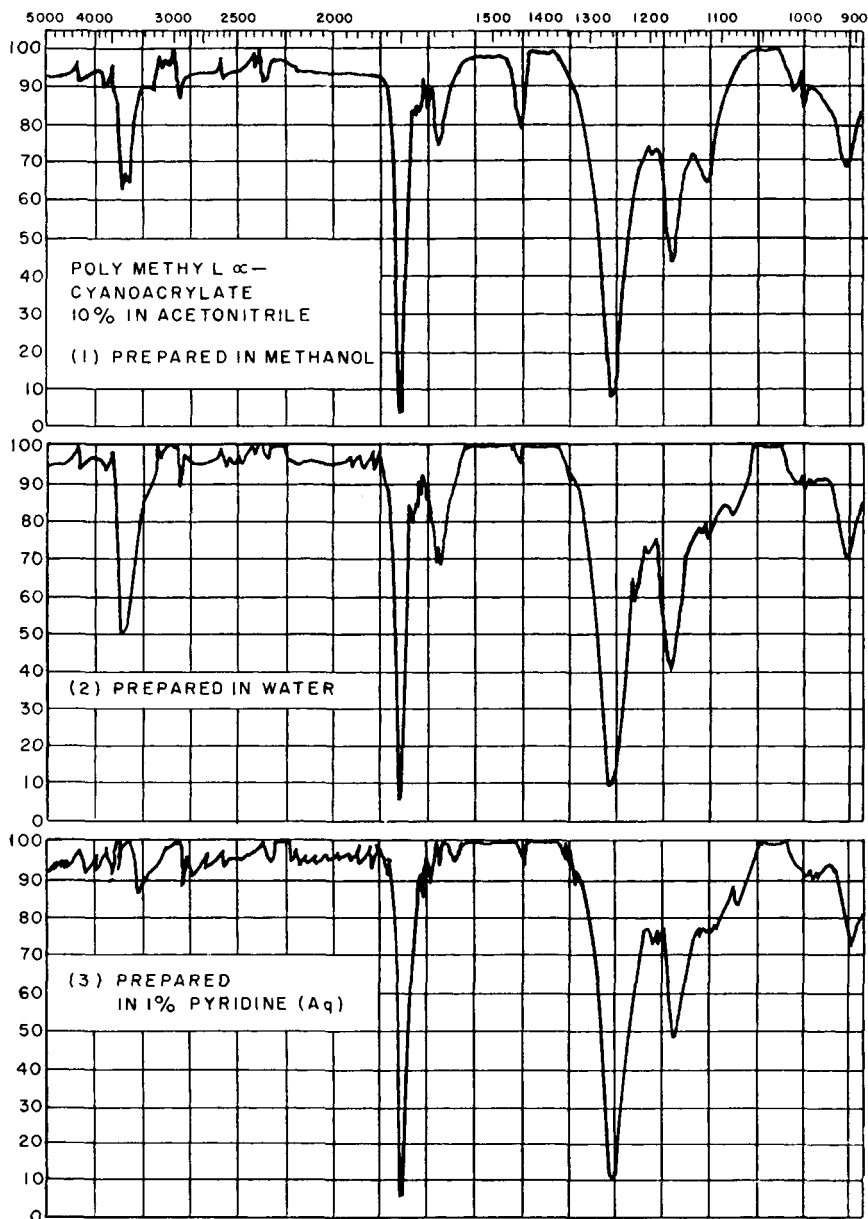


Fig. 3. Infrared spectra of poly(methyl  $\alpha$ -cyanoacrylate), 10% in acetonitrile: (a) prepared in methanol; (b) prepared in water; (c) prepared in 1% pyridine (aq.).

### Polymerization Mechanism

The proposed mechanism of polymerization in accordance with Coover and co-workers is as shown in eq. (1).

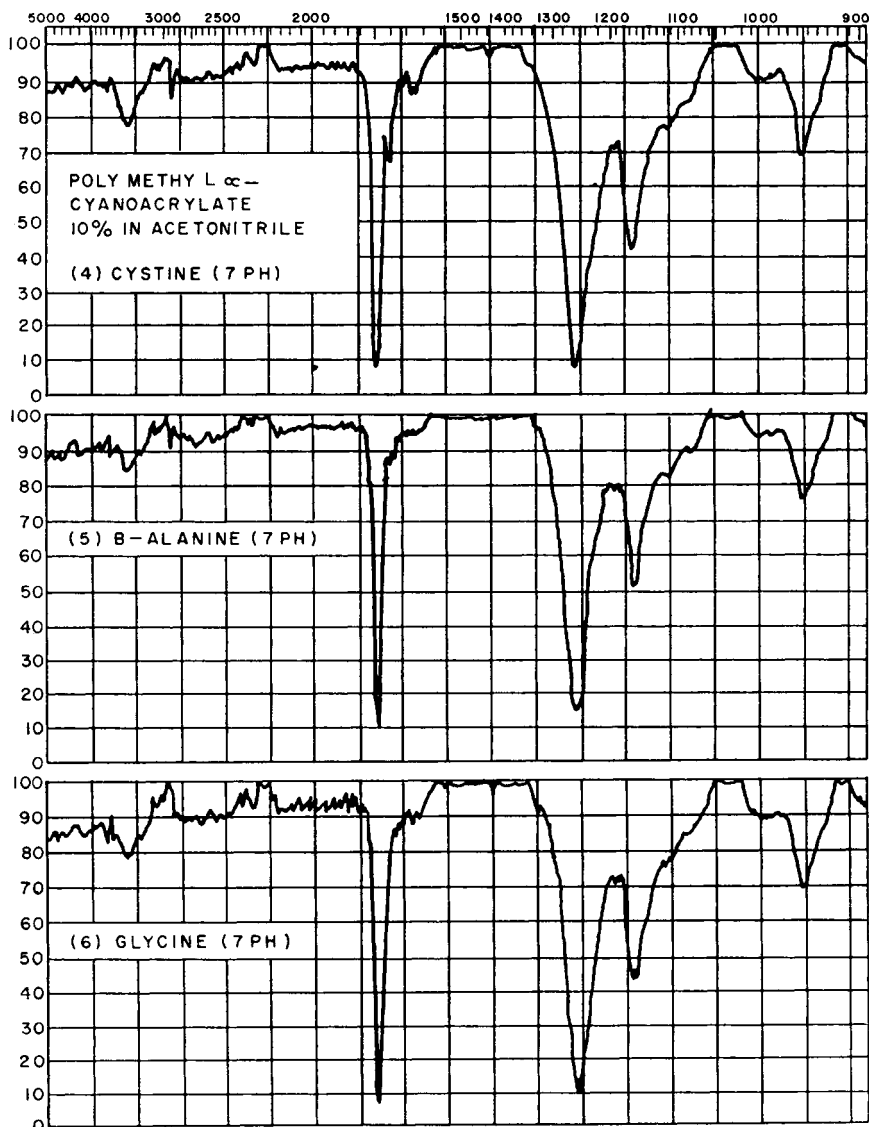
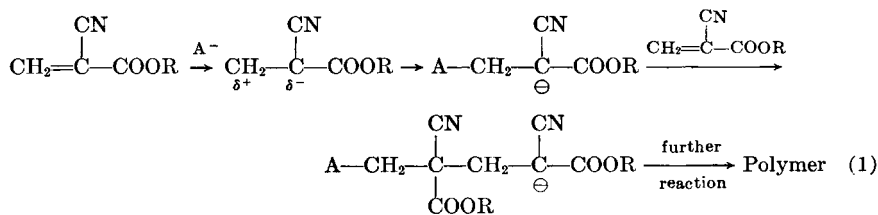


Fig. 4. Infrared spectra of poly(methyl  $\alpha$ -cyanoacrylate), 10% in acetonitrile: (a) prepared in cysteine (pH 7); (b) prepared in  $\beta$ -alanine (pH 7); (c) prepared in glycine (pH 7).





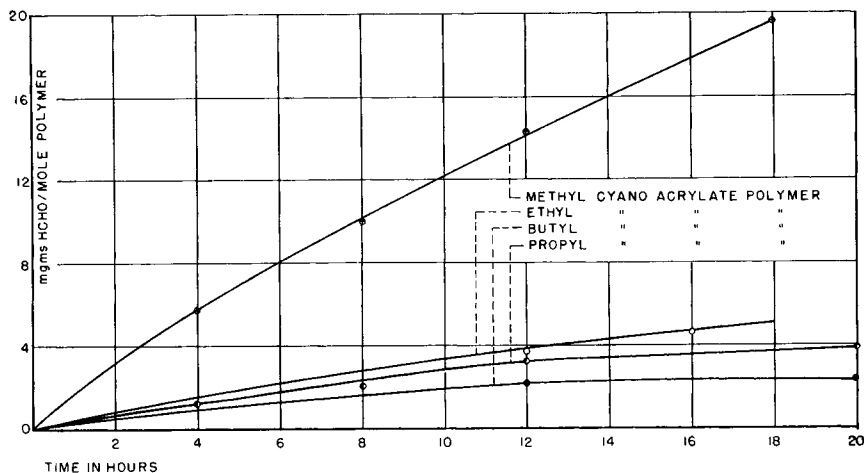


Fig. 5. Heterogeneous degradation of  $\alpha$ -cyanoacrylate polymers.

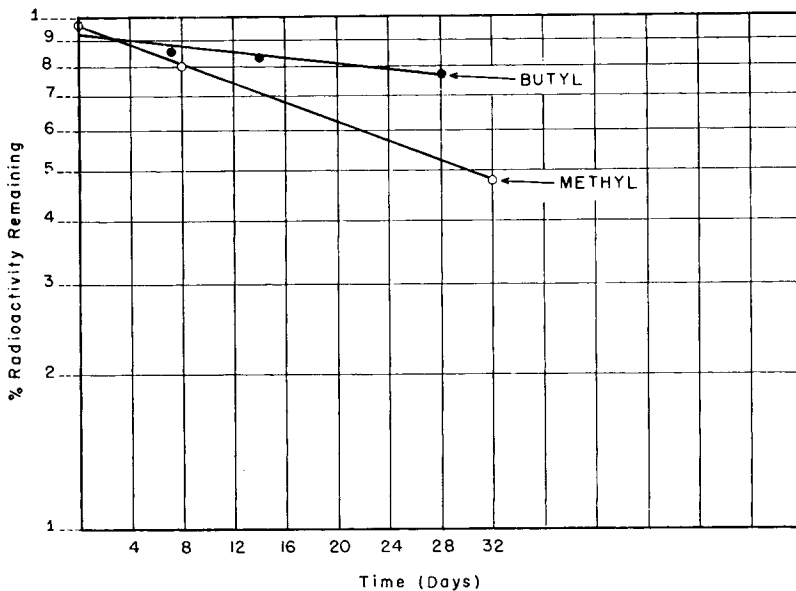


Fig. 6. *In vivo* degradation of  $\alpha$ -cyanoacrylate polymers.

The presence of the attacking nucleophile brings about strong electromeric ( $-E$ ) effects which make the nitrile and the alkoxy carbonyl group highly electronegative, thereby causing polarization of the double bond. Even weak bases, such as water or alcohol, can apparently induce such effects and initiate polymerization.<sup>8-10</sup> This mechanism requires that the base initiating species be present as an endgroup in the polymer. That such is the case is demonstrated by the infrared spectra plotted in Figures 3-6. The polymer which is prepared in water shows the presence of the

OH group at  $3600\text{ cm.}^{-1}$ . The polymer prepared in undried methanol shows a suppression of the band at  $3600\text{ cm.}^{-1}$  and the appearance of the  $\text{OCH}_3$  absorption band at  $1100\text{ cm.}^{-1}$ . These data indicate an apparent competition between the methoxy and hydroxy nucleophiles for initiation of polymerization. Polymers prepared in aqueous solutions of pyridine (Fig. 3c) and in aqueous solutions of cysteine, alanine, and glycine (Fig. 4) show substantial suppression of the OH absorption band. These data suggest that nucleophiles other than the OH may be preferentially involved in the initiation of polymerization in the presence of these amino acids, such as the  $\text{NH}_2$  groups for example. If such is the case, then the  $\text{NH}_2$  groups of protein molecules in the tissue may possibly be involved in initiating polymerization of the monomers when used *in vivo*. Such initiation could lead to primary chemical bonding of the adhesives to the tissue substrate, thereby resulting in strong bonding. Some further evidence indicative of this possibility is produced by the fact that efforts to extract the *in vivo* polymer adherent to the tissues, by the usual polymer solvents, such as nitromethane, dimethylformamide, and acetonitrile, were not successful.

### Polymer Degradation

The polymers of alkyl  $\alpha$ -cyanoacrylates degrade in the presence of water, giving rise to formaldehyde as one of the end products of the process. This has been proven by the preparation of derivatives of 2,4-dinitrophenylhydrazine and dimedone (Table I) from the aqueous extracts of the pure polymer prepared under standard conditions. Concomitantly, the production of formaldehyde is accompanied by a decrease in number-average molecular weight of the polymer. This was shown by the change in molecular weight of poly(ethyl  $\alpha$ -cyanoacrylate), 1427 to 990, when the polymer dissolved in 95% acetonitrile-5% water solution was heated at  $80^\circ\text{C.}$  for 24 hr. The same treatment converted a poly(butyl  $\alpha$ -cyanoacrylate) sample from a solid powder to an oil.

### Heterogeneous Degradation

Water-insoluble poly- $\alpha$ -cyanoacrylate powders are degraded in the presence of water with the formation of formaldehyde. The process of degradation reaches an equilibrium state, at which the amount of formaldehyde produced remains constant. This equilibrium value of formaldehyde is reached slowly at pH 7 at  $25^\circ\text{C.}$  but faster in neutral boiling water or in cold alkaline dispersion. The equilibrium can be shifted however and more formaldehyde produced by using fresh quantities of water. The results of such experiments on polymers in the homologous series presented in Figure 5, show that the rate of aqueous degradation is considerably slower for the polymers of the higher alkyl esters. Poly(methyl  $\alpha$ -cyanoacrylate) degrades much faster than others, and the diminution in the degradation rate becomes smaller in the higher members of the homologous series. These data may be compared with the results

obtained from experiments in which the disappearance of radioactivity  $\beta$ - $^{14}\text{C}$ -tagged methyl and butyl  $\alpha$ -cyanoacrylate, implanted in rats, was measured as a function of time. In Figure 6 are plotted the per cent radioactivity remaining in the implanted polymer versus time. The data show that the disappearance of the butyl polymer from the implanted site is slower than for that of the methyl polymer.

### Homogeneous Degradation

The degradation of cyanoacrylate polymers in aqueous acetonitrile, (a good solvent) is presented graphically in Figure 7 as the quantity of for-

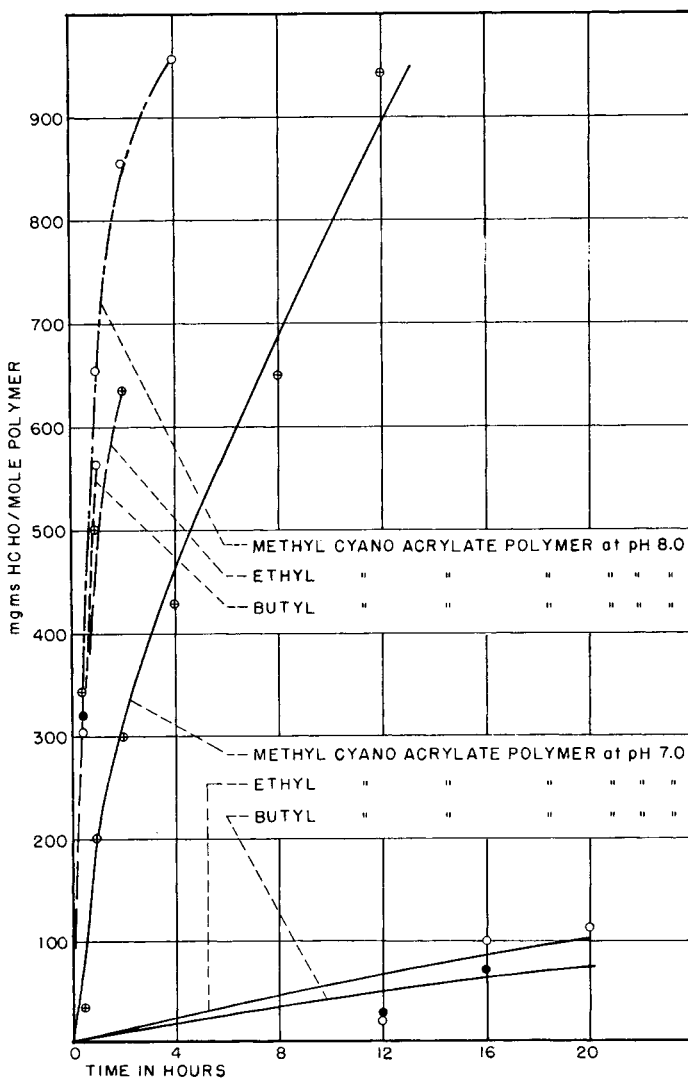


Fig. 7. Homogeneous degradation of  $\alpha$ -cyanoacrylate polymers.

maldehyde produced, plotted against time, at both pH 7 and 8. Analysis of the results shows that the degradation of polymers in large excess of water (1:14 molar ratio) obeys first-order kinetics, indicating a pseudo-unimolecular reaction. The data do not fit bimolecular reaction kinetics in the presence of a large excess of water. The rate constants calculated on the basis of the data are given in Table III, along with the  $M_n$  of the polymers concerned. It was attempted to study the kinetics of the reaction using equimolar proportions of water, but it was found that formaldehyde produced in the initial 4 hr. was very low and remained constant. Nevertheless, when large quantities of water are used, the concentration of formaldehyde is much larger, and the kinetics of the initial reaction before it reaches equilibrium could be studied. A control experiment run under the same conditions with anhydrous pure acetonitrile did not produce formaldehyde.

TABLE III  
Rates of Homogeneous Degradation of Cyanoacrylate Polymers

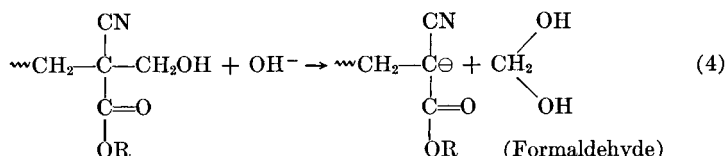
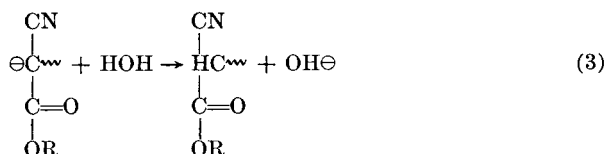
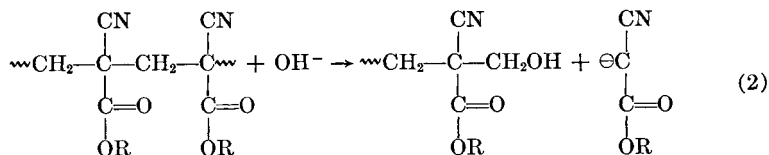
Polymer of	Number-average molecular weight	$K, \text{hr.}^{-1}$	
		pH 7	pH 8
Methyl ester	2204	$3.0 \times 10^{-3}$	$1.0 \times 10^{-2}$
Ethyl ester	1533	$2.0 \times 10^{-4}$	$1.5 \times 10^{-2}$
Butyl ester	2054	$1.0 \times 10^{-5}$	$2.0 \times 10^{-2}$

It is seen from these data that the rates of degradation in the homogeneous phase, as in the heterogeneous system, also are much larger for methyl polymer and are greatly diminished in case of the polymers of higher esters at pH 7. The rates of degradation however, remain high in alkaline solutions (pH 8) for all polymers and differ only slightly from each other (Table III). The polymer solutions at pH 8 showed a distinct yellowing tendency on refluxing, which may be indicative of a chemical reaction, perhaps intramolecular cyclization, through the cyano groups under alkaline conditions, similar to the behavior of polyacrylonitrile, which was noted by McCartney.<sup>11</sup>

### Degradation Mechanism

The aqueous degradation process is analogous to that reported by Gilbert and co-workers in case of poly(vinylidene cyanide).<sup>5</sup> These authors presume the random addition of water molecules to the polymer chain, which further degrades into a polymer fraction and formaldehyde. The same mechanism may hold for poly(alkyl  $\alpha$ -cyanoacrylate) due to the similarity in molecular structure. However, the fact that the slow degradation in neutral water is highly accelerated in the alkaline medium (see homogeneous degradation) suggests that the degradation is started by the initial attack

of the hydroxyl ion, leading to the reverse Knoevenagel reaction as shown in eqs. (2)–(4).



The carbanions formed according to this mechanism can recombine with the formaldehyde product, making the whole process reversible.

### Medical Implications

Medical evaluation of methyl  $\alpha$ -cyanoacrylate monomer as a tissue adhesive has indicated that the polymer as well as the monomer elicits acute inflammatory responses in tissues. Further medical studies with the homologous series of  $\alpha$ -cyanoacrylates prepared in this laboratory have indicated that as the homologous series is ascended, the inflammatory response is decreased. The butyl derivative and higher homologs appear to be well tolerated by the tissues. These data are in general accord with the *in vitro* studies presented in this paper. If indeed, the implanted polymers degrade *in vivo* as has been demonstrated *in vitro*, then in the vicinity of the implanted polymer particles, one may expect to find formaldehyde and an alkyl cyanoacetate (if the degradation proceeds to the ultimate stoichiometric products). Both these compounds are toxic and can elicit acute inflammatory responses. The fact that the butyl derivative is tissue-tolerated and degrades at a considerably slower rate than the methyl derivative, which is not well tolerated by the tissues, leads to the implication that the tissues can metabolize more easily the lower concentration of degradation products present at a given time in the case of the butyl derivative.

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### Résumé

En vue d'étudier les rapports entre la structure et la réactivité des tissus et en dernière analyse de développer un adhésif manifestant moins de nécrose, ce laboratoire a entrepris l'étude de la synthèse et l'étude de la dégradation d'une série homologue de monomère  $\alpha$ -cyanoacryliques et de leurs polymères correspondants. Une méthode de synthèse de cyanoacrylate de haute pureté et de certaines de leurs propriétés physiques et chimiques sont présentées. *In vitro*, des études cinétiques dans des conditions hétérogènes et homogènes indiquent que les polymères cyanoacryliques dégradent par scission hydrolytique de la chaîne polymérique. Les produits résultant de cette scission sont le formaldéhyde (identifié avec certitude par formation de ses dérivés) et finalement un cyanoacétate d'alcoyle. À mesure que la série homologue croît, la vitesse de dégradation dans des conditions neutres diminue. En solution homogène dans des solutions alcalines, la vitesse de dégradation est considérablement plus élevée que dans des conditions neutres, et la vitesse obtenue avec des dérivés méthyliques jusque butyliques sont du même ordre de grandeur. Un mécanisme est proposé pour la dégradation. L'évaluation médicale indique que, à mesure que l'on monte dans la série homologue, la tolérance des tissus s'accroît pour les monomères et les polymères. On présente également les rapports existant entre ces résultats *in vitro* et les données médicales.

### Zusammenfassung

Um die Beziehungen für die Strukturgewebe reaktivität zu untersuchen und schliesslich ein weniger nekrotisch wirkendes Klebemittel zu entwickeln, wurde in unserem Laboratorium die Synthese und der Abbau der homologen Reihe der  $\alpha$ -Cyanoacrylatmonomeren und -polymeren untersucht. Eine Methode zur Synthese von Cyanoacrylaten hoher Reinheit wird angegeben, und einige ihrer chemischen und physikalischen Eigenschaften werden beschrieben. Kinetische Untersuchungen *in vitro* unter heterogenen und homogenen Bedingungen zeigen, dass Cyanoacrylatpolymere durch hydrolytische Spaltung der Polymerkette abgebaut werden. Die bei einer solchen Spaltung entstehenden Produkte sind Formaldehyd (durch Derivatbildung identifiziert) und schliesslich ein Alkylcyanoacetat. Bei Aufsteigen in der homologen Reihe nimmt die Abbaugeschwindigkeit unter neutralen Bedingungen ab. In homogener Lösung ist die Abbaugeschwindigkeit unter alkalischen Bedingungen beträchtlich höher als unter neutralen Bedingungen, und die Geschwindigkeiten der Methyl- bis Butyllderivate sind von gleichgrosser Ordnung. Ein Abbaumechanismus wird vorgeschlagen. Die medizinische Auswertung zeigte, dass beim Aufsteigen in der homologen Reihe der Gewebeverträglichkeit der Monomeren und Polymeren zunimmt. Die Bedeutung der Ergebnisse der *in-vitro*-Untersuchungen für diesen medizinischen Befund wird gezeigt.

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