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Interfacial Polymerization of *n*-Alkyl α-Cyanoacrylate Homologs

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Synopsis

The *n*-alkyl α-cyanoacrylates from methyl through *n*-octyl exhibit a reverse order of polymerization rate on biological substrates compared to that on water. On water, the lower homologs spread and polymerize rapidly, whereas the higher homologs spread but polymerize slowly. On biological substrates, the lower homologs do not spread or spread slightly and the higher homologs exhibit large spreadabilities and very rapid polymerization rates. Determination of the spreading coefficients for these systems by using the monomers or model compounds confirm the observed spreadabilities. It is proposed that the increased rate of polymerization of the higher homologs on biological substrates may be due to increased catalyst concentrations on these surfaces or to the solubilization of the higher homologs at the interface, making the catalyst sites more available to the monomer. The suggestion is made that if the liquid monomers spread and orient on the substrate and subsequently polymerize, the polymers will maintain the orientation. If such is the case, a technique is available for preparing stereospecific vinyl polymers which may have different spatial configurations depending on the polarity of the liquid substrate upon which they have been allowed to spread and polymerize.

INTRODUCTION

For the past several years, the homologous series of *n*-alkyl α-cyanoacrylate monomers have been under study at this center as hemostasis-inducing compounds and as tissue adhesives in nonsuture closure of wounds. The monomers, which are usually stabilized with 50 ppm of SO_2, may be rapidly converted to polymers by anionic initiation. Thus, if the monomers are sprayed or added dropwise and subsequently spread out in a thin film on tissue surfaces, the nucleophiles present at the site of application initiate polymerization and polymers are formed which coat the tissue substrate.

It has been observed *in vitro* that if a drop of methyl α-cyanoacrylate is placed on distilled water in a Petri dish, a part of the monomer sinks below the surface ($d^{20} = 1.1044$) and part spreads out in a thin film on the liquid surface and within 10 sec., a white translucent film forms.

The portion of the drop that is submerged takes over 5 min. to polymerize completely. If the same experiment is carried out with the ethyl, *n*-propyl, and *n*-butyl derivatives, the spreading is not quite as large as with the

methyl derivative, but the rates of polymerization of the monomers are approximately equivalent to that of the methyl monomer. The higher homologs from *n*-amyl to *n*-heptyl spread on water but tend subsequently to form discrete droplets with the tendency increasing toward heptyl monomer. As a result, the polymerization of the higher homologs proceeds more slowly. The rates of polymerization are approximately fastest for the lower homologs (methyl to butyl) and slowest for the higher homologs. We term this effect the aqueous effect.

When the monomers were used in an experiment to stop bleeding in surgically wounded livers in dogs, by spraying the monomers against cut liver surfaces, it was observed that the rates of polymerization were directly opposite from those observed on distilled water. In this instance, the heptyl monomer was converted to a polymer film most rapidly and the methyl monomer least rapidly.

Similar results were observed when the monomers were sprayed against the cut and uncut spleen and the omentum. In all instances the monomers ranging from amyl to heptyl formed continuous polymeric films practically instantaneously against body tissues.

The methyl, ethyl, and *n*-propyl monomers appeared to form liquid puddles which gradually polymerized to solid polymeric discontinuous films which did not appear as satisfactory for achieving hemostasis as the higher homologs. This reverse effect, in which the higher homologs polymerized the most rapidly and the lower the least rapidly, we designated the blood effect.

It was decided to study these effects further, and the results of this investigation are herein reported.

EXPERIMENTAL

Monomer Preparation

The monomers, the *n*-alkyl α-cyanoacrylates from methyl to octyl, were prepared and analyzed for purity as previously described.[1] Monomers of purities of 98.5% or higher were used.

Spreadability and Polymerization Times

To observe spreadability and polymerization times, Petri dishes, 15 cm. diameter, were filled with the test fluid to within 0.25 cm. of the top, and the monomer, contained in a polyethylene bottle filled with a polyethylene dropping nozzle, was dropped on to the center of the test fluid. The tip of the nozzle was held approximately 3 mm. from the surface of the test fluid and a single drop was delivered. Spreadability was measured in centimeters, and the time for polymerization was measured from the time the monomer droplet hit the surface until the monomers appeared to be completely polymerized.

Surface and Interfacial Tension

Surface and interfacial tension measurements were carried out at 25°C. with a Du Nüoy tensiometer using a 6-cm. platinum ring.

RESULTS AND DISCUSSION

Average spreadability and polymerization time results for water and citrated blood are summarized in Table I. It is noted that in the aqueous effect, the methyl to butyl monomers show a large spread on water and rapid polymerization times, whereas the higher homologs from amyl to octyl show a large spread but longer polymerization times. By contrast, on blood, the lower members of the homologous series show small spreadabilities and long polymerization times and the higher homologs comparatively large spreadabilities and rapid polymerization times. Figure 1 pictorially demonstrates the spreadability obtained on blood plasma for the homologous series, illustrative of a typical blood effect. Since the polymerization rate in this example of interfacial vinyl polymerization may be presumed to be a function of the amount of monomer surface exposed to the substrate and the availability of the monomer to the catalyst sites present in the substrate, the higher homologs polymerize practically instantaneously and most rapidly on blood. The lower homologs which form liquid lenses and are thereby confined as bulk monomers on blood, polymerize at a considerably slower rate than the higher homologs, and polymerization times of over 300 sec. are noted.

Further work showed that typical aqueous effects were obtained with physiologic saline (0.89%), 5% dextrose in water, and lactated Ringers solution. The blood effect was obtained with dog and human blood, plasma, and serum, isotonic solution of human albumin, 1% aqueous casein solution, 1% egg albumin. A modified blood effect (no spreadability and slow polymerization for the methyl derivative and a small spread but rapid polymerization of the heptyl derivative) was obtained with 3% arginine solution whose surface tension had been adjusted to 35.9 dyne/cm. by potassium oleate solution.

Interestingly enough, a 1% aqueous gelatin solution gave mixed blood and aqueous effects, e.g., large spreadability and rapid polymerization times for both the methyl and heptyl monomers.

In order to study the aqueous and blood effects in more detail, spreading coefficients were determined for the methyl and heptyl monomer against

TABLE I

	Aqueous effect, H_2O (pH 7.1)		Blood effect, citrated blood	
Monomer	Spreadability, cm.	Polymerization time, sec.	Spreadability, cm.	Polymerization time, sec.
Methyl	20	<10	0.5	>300
Ethyl	4.5	<10	0.5	>300
n-Propyl	10	<10	2	20
n-Butyl	18	<10	5	1
n-Amyl	16	15	14	2
n-Hexyl	16	64	64	2.5
n-Heptyl	20	>300	11	2
n-Octyl	18	>300	15	4

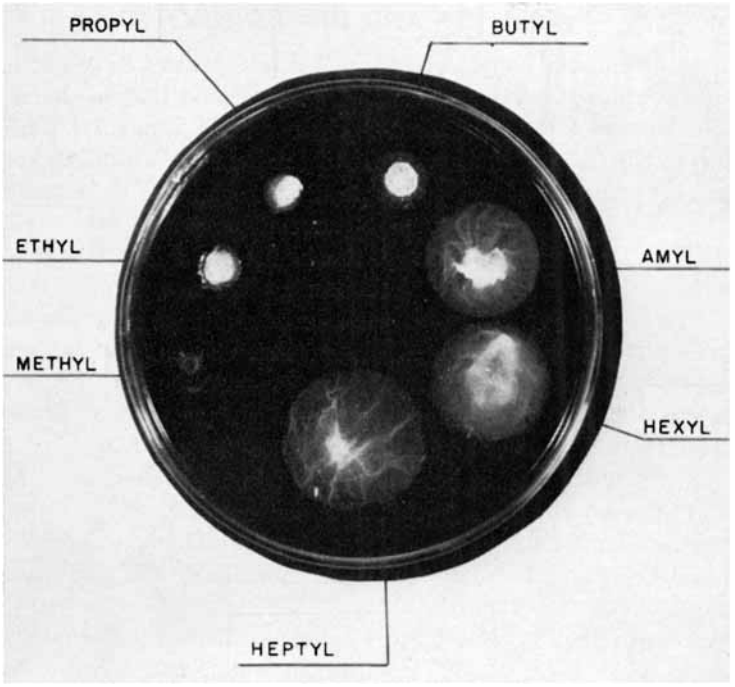

Figure 1.

water. Attempts to measure interfacial tension of these cyanoacrylates against serum or casein solutions were not successful because rapid polymerization occurred at the interface. Instead, methyl and heptyl cyanoacetates were substituted as model compounds for the cyanoacrylates in these instances. Pertinent data are summarized in Table II. The spreading coefficients (28.7 and 26.5 for methyl and *n*-heptyl cyanoacrylates and 24.9 and 27.7 for methyl and *n*-heptyl cyanoacetates) give quantitative confirmation for the observed spreading of these compounds on water. Interfacial tension values for methyl α-cyanoacrylate and *n*-heptyl cyanoacrylate of 5.7 and 16.6, respectively, may be interpreted as indicating that the mutual attraction of the methyl α-cyanoacrylate molecules for the water molecules at the interface is greater than that of the heptyl cyanoacrylate molecules for the water molecules. The greater hydrophilicity of the methyl monomer may also account for its more rapid polymerization on water than the heptyl monomer.

Spreading coefficients for methyl cyanoacetate and heptyl cyanoacetate for 1.0% casein solutions are -4.5 and $+7.4$, respectively, and -7.3 and $+5.6$ for these compounds on blood serum. Similar results may be expected from the alkyl α-cyanoacrylates on serum or 1% casein solution, as with the cyanoacetate, because the observed nonspreadability of the methyl α-cyanoacrylate and spreadability of the heptyl α-cyanoacrylate derivatives are similar to those obtained with the corresponding cyanoacetates. The spreading coefficients for methyl and heptyl monomers

TABLE II

Sample A	γ_A	Sample B	γ_B	Sample AB	γ_{AB}	Spreading coefficient $\gamma_A - [\gamma_B + \gamma_{AB}]$
			With Water Effect			
Water/air	71.4	Methyl monomer/air	37.0	Methyl monomer/water	5.7	28.7
		Heptyl monomer/air	28.3	Heptyl monomer/water	16.6	26.5
Water/air	71.4	Methyl cyanoacetate/air	42.2	Methyl cyanoacetate/water	4.3	24.9
		Heptyl cyanoacetate/air	26.8	Heptyl cyanoacetate/water	16.9	27.7
			Solutions with Blood Effect			
Casein/air	43.4	Methyl cyanoacetate/air	42.2	Methyl cyanoacetate/casein	5.7	−4.5
		Heptyl cyanoacetate/air	26.8	Heptyl cyanoacetate/casein	9.2	+7.4
Serum/air	45.4	Methyl cyanoacetate/air	42.2	Methyl cyanoacetate/serum	10.5	−7.3
		Heptyl cyanoacetate/air	26.8	Heptyl cyanoacetate/serum	13.0	+5.6
Arginine/air	35.9	Methyl monomer/air	37.0	Methyl monomer/arginine	6.0	−7.1
		Heptyl monomer/air	28.3	Heptyl monomer/arginine	7.4	+0.2
			Solutions with Blood–Aqueous Effect			
Gelatin/air	54.5	Methyl monomer/air	37.0	Methyl monomer/gelatin	4.5	13.0
		Heptyl monomer/air	28.3	Heptyl monomer/gelatin	3.4	22.8

(−7.1 and +0.2, respectively) on arginine solution confirm the observed nonspreadability for the methyl monomer and very slight spreadability for the heptyl monomer.

The interfacial tensions obtained in the blood effect solutions as well as in the case of the gelatin solution are rather close in value for both monomers. This indicates that both the methyl monomer, which is more hydrophilic, and the heptyl monomer, which is more hydrophobic, appear to be equally interacting with the protein molecules at the surface of the protein solutions. Although heptyl monomer spreads on water and blood, the heptyl monomer polymerizes slowly on water and instantaneously on blood. This result may be due to several possible factors. They are (*1*) the possibly increased concentration of initiating nucleophiles present in blood compared to water (perhaps lone pairs of electrons on the pendant amino groups in proteins may serve as nucleophiles) and/or (*2*) the protective colloid action of the protein molecules at the blood–monomer interface which may have a tendency to solubilize the monomer at the interface, thereby bringing it in closer contact with the initiating nucleophiles. The latter implies that blood presents a more hydrophobic surface to the heptyl monomer than does water. This could arise as a result of the blood proteins at the interface forming coherent, but rather amorphous films whose structures is not exactly that of the natural protein but involves partial denaturation through a spreading out of the various hydrophobic side chains in the protein molecules.[2]

The fact that the methyl monomer forms a lens and does not spread on blood is sufficient to account for its slow polymerization. Here the polymerization is limited to the surface of the droplet. The polymer that forms around the surface of the drop is self-protecting and further polymerization of the monomer is dependent upon diffusion of the nucleophiles through the protective barrier. Since it has been indicated from the interfacial tension data that the methyl and *n*-heptyl monomers are "proteinophilic," it would be expected that if the methyl monomer could spread on blood, it would polymerize rapidly as does the heptyl monomer. Such is the case for the monomer on 1% gelatin solution in which both monomers exhibit similar interfacial tensions against gelatin and both monomers spread and polymerize rapidly. Since gelatin contains glycine as its major amino acid, approximately 25%, experiments are being carried out using α-^{14}C-tagged glycine to determine whether glycine can initiate the polymerization of the *n*-alkyl cyanoacrylates and enter the growing chain as an endgroup. Previous work indicating this possibly has shown that initiation of the polymerization in aqueous glycine resulted in suppression of OH absorption in the infrared spectrum of the resulting polymer compared to the polymer prepared in distilled water.[1]

Finally, it is well known that when a long-chain alcohol or acid spreads on water, the molecules are apparently oriented in such a manner that the polar group is attached to the water with the hydrocarbon chain pointing in the opposite direction. If, in a similar manner, the monomers described in this study spread on a liquid substrate and are presumed to orient and

subsequently polymerize, it is possible that the polymer will maintain its liquid film orientation. If such is the case, a technique is available for preparing stereospecific vinyl polymers which may have different spatial structures depending on the polarity of the liquid substrate upon which they have been allowed to spread and polymerize. Such studies are under way in this laboratory.

References

1. F. Leonard, R. K. Kulkarni, G. Brandes, J. Nelson, and J. J. Cameron, *J. Appl. Polymer Sci.*, **10**, 259 (1960).

2. A. W. Adamson, *Physical Chemistry of Surfaces*, Interscience, New York, 1960, p. 396.

Résumé

Les α-cyanoacrylates d'alcoyle normal depuis méthyle jusque octyle normal montrent un ordre de vitesse de polymérisation inverse sur des substrats biologiques et sur l'eau. Sur l'eau les homologues inférieurs s'étalent et polymérisent rapidement alors que les homologues supérieurs s'étalent mais ne polymérisent que lentement. Sur des substrats biologiques par contre, les homologues inférieurs ne s'étalent pas, alors que les homologues supérieurs manifestent un étalement appréciable et présentent des vitesses de polymérisation très élevées. La détermination du coefficient d'étalement pour ce système utilisant des monomères ou des composés modèles confirment les étalements observés. On propose que l'accroissement des vitesses de polymérisation des homologues supérieurs sur des substrats biologiques pourrait être dû à une augmentation de concentration en catalyseur à leurs surfaces ou à la solubilisation des homologues supérieurs à l'interface, rendant les sites catalytiques plus accessibles au monomère. La suggestion est faite que, si les monomères sont étalés et orientés sur les substrats et polymérisent ultérieurement les polymères maintiendront cette orientation. Si tel est le cas, une technique est disponible pour préparer des polymères vinyliques stéréo-spécifiques, qui pourraient avoir des configurations spatiales différentes suivant la polarité du substrat liquide sur lesquels ils ont été étalés et soumis à polymérisation.

Zusammenfassung

Die *n*-Alkyl-α-cyanoacrylate von Methyl bis *n*-Octyl zeigen auf biologischen Substraten die umgekehrte Reihenfolge der Polymerisationsgeschwindigkeit wie auf Wasser. Auf Wasser werden die niedrigeren Homologen gespreitet und polymerisieren rasch, während die höheren Homologen gespreitet werden, aber langsam polymerisieren. Auf biologischen Substraten werden die niedrigeren Homologen nicht oder nur schwach gespreitet, und die höheren Homologen zeigen eine grosse Spreitbarkeit und sehr grosse Polymerisationsgeschwindigkeiten. Die Bestimmung der Spreitungskoeffizienten dieser Systeme mit Monomeren oder Modellverbindungen bestätigt die beobachteten Spreitbarkeiten. Es wird abgenommen, dass die erhöhte Polymerisationsgeschwindigkeit der höheren Homologen auf biologischen Substraten durch die erhöhte Katalysatorkonzentration an diesen Oberflächen oder auf die Solubilisierung der höheren Homologen an der Grenzfläche, wodurch die katalytisch wirkenden Stellen dem Monomeren besser zugänglich gemacht werden, zurückzuführen ist. Es wird für Möglich gehalten, dass bei einer Spreitung der flüssigen Monomeren und einer Orientierung auf dem Substrat bei der darauffolgenden Polymerisation die Polymeren die Orientierung beibehalten werden. Wenn dies der Fall ist, so ist damit ein Verfahren zur Darstellung stereospezifischer Vinylpolymerer gegeben, welche je nach der Polarität des flüssigen Substrats, auf welchem sie gespreitet und polymerisiert werden, verschiedenartige räumliche Komponenten besitzen können.

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