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MECHANISM OF N-CARBOXY-α-AMINO ACID ANHYDRIDE (NCA) POLYMERIZATION

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The three classical mechanisms known for the polymerization of N-carboxy-α-amino acid anhydrides by basic initiators (protic and aprotic amines, basic salts) were analyzed and the discrepancies existing between what the given mechanism theoretically expects and the experimental results of the actual polymerization were examined. It was thus shown that the apparently simplest polymerizations involve secondary mechanisms with various significance besides the principal one.

Thus, all the results of the primary amine initiated polymerization do not agree with the "normal" polymerization mechanism. In many cases, the presence of carbamate end group affects the kinetics of polymerization. The coexistence of two mechanisms (the present one and the "activated monomer" mechanism) in the secondary amine initiated polymerization is well known.

It was pointed out that nearly all the results in favor of Blout's mechanism are those obtained in the presence of a great excess of the conjugate acid of the initiator or other very weak acid, and that those found in their absence rather tend to prove the contrary. However, the presence of carbamate group and its reactivity were demonstrated for both cases. The mechanism was improved for some details in order to account for the maximum of results.

Although the "activated monomer" mechanism is nearly unanimously accepted for the tertiary amine and alkali halide catalyzed polymerizations, the reactions do not involve exclusively this mechanism. The polymerization of sarcosine NCA in the presence of protic additives (or even in their absence) proceeds, as far as the propagation is concerned, at least in part by Blout's mechanism. Furthermore, it was shown that the addition of some model compounds of the growing chain (1-acetyl 3-methylhydantoin, 3-acetyl oxazolidone) to the reaction mixture of α-aminoisobutyric acid NCA and sodium methoxide initiator gives at the same time acceleration and depression effects, which suggests the coexistence of both mechanisms.

These results indicate that all three mechanisms exist with different significance in the actual polymerizations. Thus, we are led to admit an acid-basic equilibrium (very fast reaction) between the acidic NCA and the basic initiator giving the NCA salt and the conjugate acid of the initiator, and to assume the initiations (less fast reactions) by the action of all the nucleophilic species implicated in it : the conjugate acid (non-ionic nucleophile), the initiator anion, and NCA anion. Whichever is the mode of initiation, carbamate group is formed on the resulting chain end and remains as such up to the limit of concentration tolerated by the basicity of the reaction mixture. The surplus decarboxylates into a free amino end group.

In the propagation, three mechanisms – aminolytic mechanism, carbamate anion mechanism and NCA anion mechanism, operate with a significance which depends on the concentration (which is principally a function of the basicity of the reaction mixture) and the nucleophilicities of the active species concerned. A new acid-basic equilibrium sets up between all the ionic species present – the initiator anion, carbamate anion and NCA anion, and governs the permanent state of the polymerization. However, the cross-over reactions due to the attacks of the nucleophile of one mechanism on the electrophilic site of another appear in consequence to the coexistence of three mechanisms.

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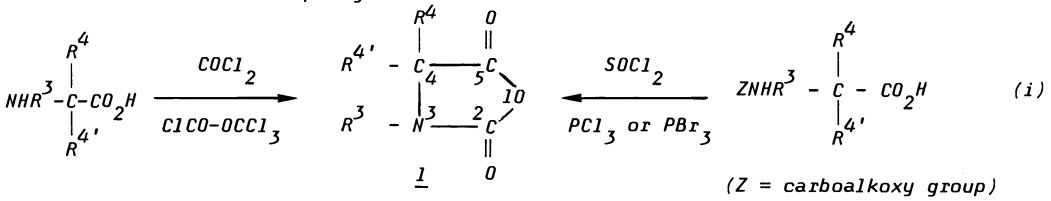
The significance of each mechanism was evaluated according to the nature of NCA (acidity) and the initiator (basicity) used.

1. INTRODUCTION

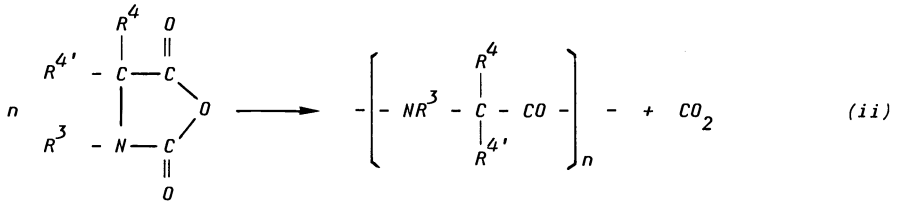
1.1 NCA Polymerization

N-Carboxy-α-amino acid anhydrides, currently called NCAs, were first described by LEUCHS (Ref. 1) in 1906 and are known under the name of Leuchs' anhydrides. They correspond to unsubstituted and substituted oxazoline-2,5-diones. They are generally synthesized by the cyclization of the N-carboalkoxy derivatives of the parent amino acids (Ref. 2), by the direct phosgenation of the amino acids (Ref. 2), or by the action of trichloromethyl chloroformate instead of phosgene (Ref. 3).



(i)

Their polymerization yields the corresponding poly-α-amino acids or polypeptides, releasing carbon dioxide gas from 1-O and 2-CO :



(ii)

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The polymerization of NCAs has been the subject of a number of review papers (Ref. 4-10). The reaction can be obtained by various means, namely (1) spontaneously or by heating, (2) by the action of protic or aprotic bases (water, alcohols, amines, alkali halides, basic salts), (3) by the action of non-alkaline organometallic compounds, (4) in liquid hydrogen fluoride. Apart from hydrogen fluoride in which the polymerization probably proceeds through a stepwise polycondensation mechanism (Ref. 11), the other means of polymerization seem to involve the anionoid or anionic mechanisms, which will be the subject of our present paper. However, we will exclude from the discussion the spontaneous, thermal polymerization whose initiation mechanism requires further investigations, and the polymerization by non-alkaline organometallic compounds which, although probably due in part to the basicity of the reaction mixture, would involve principally a mechanism proper to this type of catalysts. Our discussion will be limited to the purely chemical aspects of the actual base initiated polymerization of NCAs. The stereochemical aspects of the polymerization will be discussed on another opportunity.

1.2. Present Situation of the Mechanism Studies

A great number of experimental facts have been accumulated in the literature on the polymerization of NCAs under various conditions. In their interpretation, most authors seem to agree on the "normal" polymerization mechanism and the "activated monomer" mechanism proposed respectively for the polymerizations using primary and tertiary amines (alkali halides in dimethylformamide solution behave similarly to the latter amines from the point of view of the mechanism) and on the coexistence of the two mechanisms for the secondary amine initiated polymerization. A quantity of evidence of the nature to justify these mechanisms prompted them to consider that they are the sole operative and to exclude a priori the possibility that other mechanisms coexist. In fact, they leave some experimental results unexplained and the simplicity of the mechanisms is only an appearence.

The situation is somewhat different for the basic salt initiated polymerization, for which two conflicting mechanisms have been defended one against the other. They are the above mentioned "activated monomer" mechanism by NCA anion, first conceived by Ballard, Bamford and Block (Ref. 12-14) and later supported by Szwarc (Ref. 15), and the so-called Blout's mechanism by carbamate anion, initially proposed by Idelson and Blout (Ref. 16). It is interesting to note a peculiar feature of this long controversy in that not only the opinions of the various authors, but also the experimental evidence on which they were based, are often conflicting. Here again, we have many problems left unsolved, and we feel that

each of the proposed mechanisms describes only a part of the reality.

Thus, in order to understand better the mechanism of the base initiated polymerization of NCAs, it is more urgent to identify the origin of the disagreements at the level of the experimental results and to reexamine every proof related to the classical mechanisms at the level of the interpretation, than to try to add a few other experimental results of the same kind and to increase the confusion.

In the present paper, we are going to try an approach of the problem with a strategy completely different from that adopted by most authors. Thus, instead of attempting to deduce a reaction mechanism on the basis of this experimental result or that without taking into account the others which often contradict it, we admit *a priori* the presence in the reaction mixture, in more or less significant ratios, of all the ionic and non-ionic species whose existence was proved in specified polymerizations. Then, we assume the presence with more or less significant rates of all the reactions theoretically possible between them. Thus, starting with the hypothesis of an acid-basic equilibrium between the monomer and the basic initiator (Ref. 17), we construct a complex system of equilibria of the ionic species existing in the actual polymerization mixture in its steady state. It will be shown in this way that the hypothesis of coexistence of three polymerization mechanisms allows to account for most part of the experimental results reported until now in the literature.

2. EVIDENCE FOR AND AGAINST THE CLASSICAL MECHANISMS

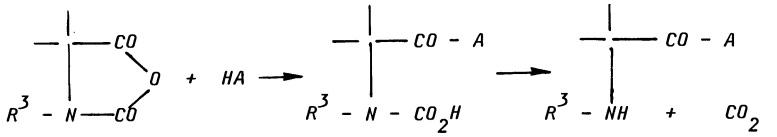
The present section will be consacrated to the analysis of the classical mechanism which have been believed to operate in the base initiated polymerization of NCAs according to the nature of the initiators used. It will be shown that each of them does exist indeed but that it deviates more or less from the actual polymerizations concerned. The discrepancies existing between what the adopted mechanism theoretically expects and the experimental results suggest that the actual polymerization does not involve a single mechanism.

2.1. "Normal" Polymerization Mechanism

This mechanism (Ref. 4) is generally admitted for the polymerization by use of the non-ionic initiators having at least one mobile hydrogen atom, such as water, alcohols, primary and secondary amines. The initiators act directly as nucleophiles and, consequently, are incorporated into the resulting polymer chains as chain initiators. This is the non-ionic (anionoid) version of Blout's mechanism (see paragraph 2.2) and it is characterized by the fact that the active species are non-ionic (molecular) nucleophiles and that the polymerization has a stepwise mechanism.

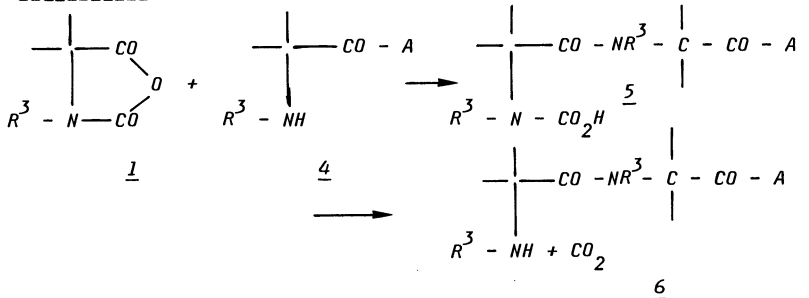
2.1.1. Reaction scheme

(1) Initiation : it is the nucleophilic attack of the initiator on 5-CO of the NCA monomer. The resulting carbamic acid decarboxylates to give the free amino group and to release carbon dioxide from 1-O and 2-CO.



1 3 4 (iii)

(2) Propagation : the resulting amino end group behaves in the same way.



1 4 5 6 (iv)

This mechanism applies as well to N-unsubstituted NCAs ($R^3 = H$) as to N-substituted NCAs ($R^3 \neq H$).

Reaction (iii) is not cationic even if the initiator HA is weakly acidic, like water and alcohols, but is due to the nucleophilic attack of the basic hetero-atom, carrier of the labile hydrogen. The intermediate carbamic acid decarboxylates immediately to give a free amino group. The propagation proceeds in the same way. The polymerization by this mechanism is generally slow.

2.1.2. Nucleophilicity of protic amines

Fuchs (Ref. 18), Wessely et al. (Ref. 19, 20) and Hanby et al. (Ref. 21) reacted NCAs with a great excess of amines and alcohols and obtained respectively the corresponding amino acid amides and esters. However, it was later shown (Ref. 22) that the reaction of protic amines with NCAs can yield both a ureido acid through an attack on 2-CO and the corresponding amino amide through an attack on 5-CO. The course of the reaction depends on the steric requirements of the amine, its concentration and its basicity.

In the actual polymerizations, the presence of the initiator fragment incorporated in the polymer was unequivocally demonstrated independently by Peggion et al. (Ref. 23) and Goodman et al. (Ref. 24), and this is a powerful proof of the mechanism. However, their incorporation ratio varies much with the structure of the initiator, from total for the relatively simple primary amines (for example : isopropylamine) to nearly 10 % for diisopropylamine, one of the secondary amines having bulky substituents. With n-hexylamine, a typical primary amine, the incorporation is of the order of 50 % (Ref. 24). In fact, two reasons explain these values : first, side reactions take place particularly at the stage of initiation, leading to the loss of a part of initiator (see paragraph 2.1.4) and, second, the part of the "normal" polymerization mechanism decreases to the profit of the "activated monomer" mechanism according to the basicity (Ref. 25) and/or the steric factors (Ref. 25 - 27) of the initiator used and the dissociating power of the solvent (Ref. 28).

2.1.3. First order kinetics

In general, the current primary amines are believed to be more nucleophilic than the amino end group of the terminal amino acid unit, hence $k_i > k_p$, where k_i represents the rate of initiation and k_p the rate of propagation. When this is the case, neither the nucleophilicity, nor the basicity of the initiator influence the course of the polymerization and the reaction must present a first-order kinetics. Waley and Watson (Ref. 29) studied the kinetics of the primary amine initiated polymerization of sarcosine NCA and verified the first-order rate in the later stages of the reaction. They explained the deviation in the initial phase (for nearly one third of the period) of the reaction by the "inclusion of an equilibrium constant in the kinetic scheme".

Ballard and Bamford (Ref. 30) pointed out the peculiar kinetic features of the polymerization of sarcosine NCA in nitrobenzene, in that it is subject to the catalytic effect of the carbamic acid formed by the reaction of the chain end and carbon dioxide. The effect disappeared when sarcosine NCA was polymerized in dimethylformamide (Ref. 31). They explained the fact by the acidic nature of the latter solvent reducing the stability of carbamic acid. The same authors (Ref. 30) obtained a first order reaction from the very beginning of the reaction when they polymerized DL-phenylalanine NCA and DL-leucine NCA in nitrobenzene using sarcosine oligomer as the initiator.

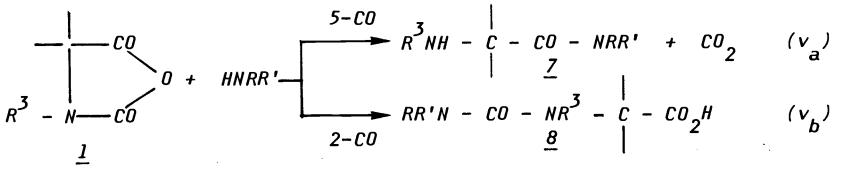
By polymerizing γ-benzyl-L-glutamate NCA and ε-carbobenzoxy-L-lysine through the initiation by diethylamine in dimethylformamide, Shalitin and Katchalski (Ref. 32) found a first order rate. However, these NCAs presented a peculiar kinetic behavior in apolar solvents. Thus, Doty and Lundberg (Ref. 33), on the one hand, and Idelson and Blout (Ref. 34), on the other hand, noticed a two-stage kinetics for the n-hexylamine initiated polymerization of γ-benzyl-L-glutamate NCA in dioxane. A slow first order rate k_{2a} characterizing the initial 20 - 40 % conversion was followed by a faster first order rate k_{2b} for the rest of the polymerization, with $k_{2b} = 5\ k_{2a}$. Ballard and Bamford (Ref. 35) first doubted these results but, on repeating the experiments, finally admitted (Ref. 36) a small difference of rates of the order of $k_{2b} = 2\ k_{2a}$. Later, Elias et al. (Ref. 37) observed a slightly perceptible positive or negative effect of carbon dioxide on the n-hexylamine initiated polymerization and copolymerization of γ-benzyl-L-glutamate NCA and pointed out the possible role of carbamate group in the reaction. They attributed the difference of the results obtained by Doty, Blout and their collaborators and those reported by Bamford's team to the difference of their experimental procedure, the former authors operating without removal of the released carbon dioxide and the latter workers under constant pressure of carbon dioxide gas. Later, Rinaudo and Domard (Ref. 38) studied the ethylamine initiated polymerization of γ-benzyl-L-glutamate NCA and concluded to the second order kinetics with respect to the introduced initiator, which led them to assume the formation of the carbamate salt of two polymer chains as the molecular growth intermediate. The problem of presence of carbamate groups in the reaction mixture will be treated in paragraph 2.2.5. The fact that in the above examples the partial shielding of the active amino end groups accelerates the polymerization suggests the coexistence of a faster polymerization due to carbamate groups, i.e. Blout's mechanism, besides the "normal" polymerization mechanism. Its part can be

fairly great in the polymerization of sarcosine NCA, in which a secondary amino group is the propagating species. We believe that Blout's mechanism is not to be ruled out *a priori* for any protic amine initiated polymerization as a secondary mechanism, especially since the coexistence of the "activated monomer" mechanism is generally ackowledged for the secondary amine initiated polymerization.

2.1.4 Reactions of termination

The first order kinetics, discussed above, is obtained only when the reactions of termination are completely absent. This was shown by Waley and Watson (Ref. 29) to be the case with the polymerization of sarcosine NCA initiated by the amino end groups of a preformed, low molecular weight polysarcosine. Block copolymers could be obtained by this method using a second monomer other than sarcosine NCA.

However, a secondary reaction due to the attack of 2-CO by the amino group and leading to the formation of ureido acid type chain end is not totally absent (Ref. 39), in particular in the reaction of initiation (Ref. 40). It is known that the higher the basicity of the amine used, the greater the part of the wrong reaction (Ref. 41). Since the amino end groups of the growing chains are generally less basic than the initiator amine, the chains once grown beyond the stage of oligomers are scarcely subject to this type of termination. Katchalski et al. (Ref. 42) estimated that the termination constant does not exceed a small percentage of the propagation constant, and Goodman and Hutchison (Ref. 24, 43) reported a value of 0.15 % for their n-hexylamine initiated polymerization of C^{14}-labeled γ-benzyl-L-glutamate NCA. It is worthwhile noting in the above discussion that the significance of the wrong reaction changes subsequently to the change of the reaction conditions with time.



Other modes of termination due to the formation of hydantoin ring on the chain end (Ref. 39, 44, 45) or by the reaction of the growing chain end with under-reactive substituents (Ref. 46 - 48) have been described in the literature.

2.1.5 Molecular weight distribution

Schematically, when a polymerization has a strictly first-order kinetics, *i.e.* when all the chains start at the same time and no reaction of termination is present, a very sharp molecular weight distribution should obligatorily result. Ballard and Bamford (Ref. 30) treated mathematically such a case and demonstrated that for large DP_n the distribution of molecular weights is Poissonian. A system including termination reactions by the attack of 2-CO was treated by Katchalski et al. (Ref. 42). Coombes and Katchalski (Ref. 49) studied the polymerization presenting the two-stage kinetics discussed in paragraph 2.1.3.

Waley and Watson (Ref. 29) obtained effectively a narrow Poissonian type distribution for their polysarcosine from a polymerization initiated by sarcosine oligomer. The number average degree of polymerization corresponded well to the value given by the monomer/initiator ratio and the DP_n of the starting oligomer. Some other autors (Ref. 50, 51) also concluded to a monodispersity of their polymers.

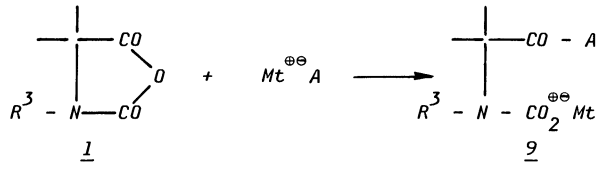
Several results leading to an opposit conclusion are also known. Sober (Ref. 52) observed a bimodal distribution in the polylysine obtained from a butylamine initiated polymerization in dimethylfoimamide. Doty and Lundberg (Ref. 33) found a very high polydispersity of DP_w/DP_n up to 8.5 for the polymer of γ-benzyl-L-glutamate NCA prepared in dioxane. A study by column fractionation conducted by Cosani et al. (Ref. 53) revealed the presence of two distinct maxima in the distribution of molecular weights, at $DP \simeq 5$ and $DP \simeq 135$, with a polydispersity of 7 to 8, for the same polymer prepared by the isopropylamine initiation in dioxane.

2.2. Blout's Mechanism

This is the ionic version of the foregoing "normal" polymerization mechanism, with the anionic moiety of the initiator salt acting as a nucleophile and playing the role of chain initiator. The mechanism was first proposed by Idelson and Blout (Ref. 16) to account for the polymerization of NCAs initiated by sodium methoxide. It disputes the legitimacy with the "activated monomer" mechanism (see Section 2.3) for the basic salt initiated polymerization of NCAs.

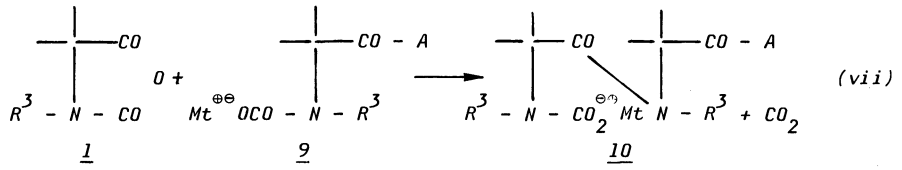
2.2.1 Reaction scheme

(1) Initiation : it is the nucleophilic attack of the anionic moiety of the basic salt initiator on NCA monomer, followed by the ring opening. No decarboxylation takes place.



(vi)

(2) Propagation : the resulting carbamate anion behaves in the same way and releases a molecule of carbon dioxide at the time of the reaction.



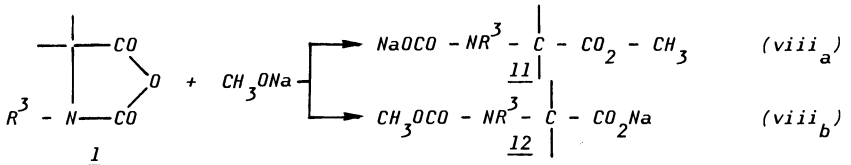
(vii)

The mechanism applies as well to N-unsubstituted NCAs (R^3 = H) as to N-substituted NCAs ($R^3 \neq$ H), since the reaction does not require the proton. It implies the incorporation of the initiator moiety in the resulting polymer chain, and the constant presence of the carbamate end group. Moreover, there should be formed as many polymer chains as the number of moles of the basic salt initiator, i.e. DP_n = (monomer consumed)/(initiator)$_o$, and the polymerization should present a first order kinetics.

Some ones of these items have been effectively proved, which provides indeniable arguments in favor of the present mechanism. However, others failed to give the expected results, showing that it is far from being the principal mechanism in certain polymerizations. Lastly, some problems have remained unsolved since the experimental results were either undecisive or conflicting.

2.2.2 Model reactions of NCA with basic salts

It was shown that the reaction of NCA with an equivalent amount of sodium methoxide yields mixtures of sodium salt of N-carboxy-α-amino acid methylester 11 and sodium salt of N-carbomethoxy-α-amino acid 12 with various proportions (Ref. 40, 54, 55). Katchalski's school (Ref. 54) used the reaction for the titration of NCAs.

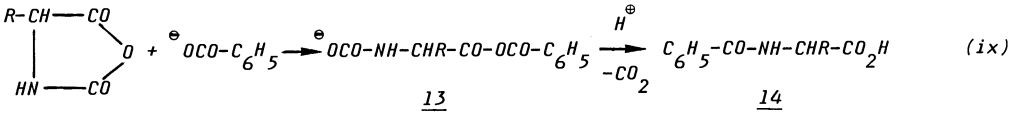


Ballard and Bamford (Ref. 56) remarked that these salts are not formed since sodium methoxide is a strong catalyst of the NCA polymerization and that the titration determines just the quantity of carbon dioxide liberated by the polymerization. In fact, a small, but significant difference should be noted between their experimental techniques. Katchalski's school often uses sodium methoxide in methanol solution, according to the preparation reported by Berger et al. (Ref. 54), while Bamford's team always manipulates under aprotic conditions. We shall see later that the addition of the conjugate acid of the basic salt initiator modifies an acid-basic equilibrium and increases the part of the initiation by Blout's mechanism.

2.2.3 Incorporation of the initiator moiety

2.2.3.1 N-unsubstituted NCAs (R^3 = H) Blout's mechanism assumes for the initiation the attack of initiator anion on the monomer unit which will be the first unit of the resulting chain.

Avny and Zilkha (Ref. 57 - 59) grafted polypeptide chains with good yields on cellulose derivatives, e.g. partially acetylated cellulose, polyvinyl alcohol and starch. Miwa and Stahmann (Ref. 60), studying the polymerization of leucine NCA in the sodium benzoate buffered aqueous solution, isolated benzoyl leucine and assumed an initiation giving mixed anhydrides of N-carboxyamino acid and benzoic acid by the attack of benzoate on the monomer:



13 14 (ix)

However, results leading to the opposite conclusion are also known in the literature. Using fluorenylpotassium as an initiator, Goodman and Arnon (Ref. 61, 62) demonstrated the non-incorporation of fluorenyl group in the resulting polymer. This is not surprising in view of the extremely weak acidity of fluorene; the very highly basic fluorenyl anion would instantaneously react with any protic compound - which can be NCA, - without giving a nucleophilic reaction.

The opinions of various authors are much divided concerning the incorporation or non-incorporation of alcoholate residue in the polymer resulting from the sodium methoxide initiation. Using C^{14}-labeled sodium methoxide diluted in methanol, Goodman and Arnon (Ref. 61, 62) proved a nearly absolute absence of the radioactivity in the polymer precipitated from the reaction mixture. Later, Goodman and Hutchison (Ref. 24) noticed that the experiments of the above work were completely meaningless on account of the use of "cold" methanol for the dilution, and resumed the work using C^{14}-labeled sodium methoxide under solid form. Again, their results indicated a quasi-absence of the built-in initiator moiety. In contrast to these results, Seeney and Harwood (Ref. 63) found up to 100% of initiator moiety incorporated in the resulting polymer, as determined by the NMR technique. To complicate still the problem, their determination was contested by Kricheldorf (Ref. 64). Recently, Goodman et al. (Ref. 65) attributed a possible presence of a small amount of incorporated initiator moiety (methoxy group in the cited work) to the reaction of methanol with a part of the N-acytaled NCA end units of the growing chains, i.e a termination reaction. They assume in this work the total absence of sodium methoxide.

It is worthwhile noting that all the results reported in support of Blout's mechanism were obtained in the presence of an excess amount of hydroxyl groups (water, alcohols, cellulosic hydroxyls, etc.). It is interesting to imagine what results Goodman and Arnon would have found if they had diluted their C^{14}-labeled initiator with "hot" methanol.

The controversies on the incorporation or non-incorporation of the benzyl group from the benzylcarbamate initiator will be examined in paragraph 2.2.5.2.

2.2.3.2 *N-substituted NCAs.* Unlike the "activated monomer" mechanism (see paragraph 2.3) which intrinsically conflict with the polymerization of N-substituted NCAs ($R^3 \neq H$), Blout's mechanism accept in principle the reaction if it can proceed without the participation of proton as described in paragraph 2.2.5.3.

Experimentally, a number of results approve this mechanism. Using sodium methoxide initiator, Fasman and Blout (Ref. 66, 67) polymerized sarcosine NCA and proline NCA into high molecular weight polymers. Overberger and David (Ref. 68) polymerized cis-5-methyl proline NCA with the same initiator. On the contrary, Goodman and Arnon (61, 62), using a C^{14}-labeled sodium methoxide initiator, obtained polymers in which they did not detect any trace of radioactive initiator moiety. Accordingly, they tried to explain the fact of the polymerization by a hypothetical deprotonation on 4-CHR position of NCA (on α-carbon atom of the amino acid). Later, Goodman and Hutchison (Ref. 24) noticed the error of the above work to have used the marked initiator in a "cold" methanol solution and repeated the experiments using a solid catalyst, to find a large percentage of the radioactivity in the polymer. Goodman and Peggion (Ref. 69) acknowledged that the chain growth was effected by carbamates in this case.

The interpretation that Bamford and Block (Ref. 70) prefer is based on the hypothetical deprotonation of the monomer on 4-position. It will be examined in paragraph 2.3.2.3. together with that on the results of the tertiary amine catalyzed polymerization, which appear as a whole to point also to the propagation by Blout's mechanism, although other types of mechanism are assumed for the initiation.

2.2.4 *Cation and anion effects*

Since Blout's mechanism initiates the polymerization by the attack of the initiator anion and since the initiation is slower than the propagation (see below in paragraph 2.2.6), it is expected that the higher the dissociation constant of the initiator salt, the faster the polymerization.

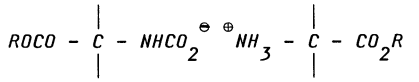
The cation effect, observed by Idelson and Blout (Ref. 16), shows it clearly and seems to approve this mechanism. In fact, the same effect would fit the "activated monomer" mechanism, as well. As to the anion effect, it is evident that in Blout's mechanism the stronger the nucleophilicity of the anion, the faster the polymerization. However, the

results reported by Sekiguchi and Doussin (Ref. 17) indicate the contrary. Certainly, one could assume that the basicity and the nucleophilicity orders are completely inversed for lower primary, secondary and tertiary alcoholate anions, or point out that the dissociation constant of the salt decreases when the basicity of its anion increases. But, it should be noted that sodium acetate is not a more efficient initiator than sodium alcoholates. The results, which apparently conflict as well with the present mechanism as with the "activated monomer" mechanism, could finally be explained when the influence of the conjugate acid of the initiator was discovered.

To be exact, it is Idelson and Blout (Ref. 16) who first detected the influence of the coexisting methanol on the sodium methoxide initiated polymerization of γ-benzyl-L-glutamate NCA. But, they did not attach any importance to the phenomenon, since "the 25-fold increase in methanol concentration only doubled the rate of polymerization". Sekiguchi and Doussin (Ref. 17) pointed out the effect of the conjugate acid of the basic initiator on the basic salt initiated polymerization, and in particular showed the remarkable influence of the addition of methanol and other protic compounds on the rate of polymerization of α-aminoisobutyric acid NCA. Assuming an acid-basic equilibrium between the acidic NCA and the basic initiator, they interpreted these results with the help of Blout's mechanism (see Section 4).

2.2.5 Role of carbamate anion

2.2.5.1 Presence of carbamate group. Although free carbamic acid is too unstable to be isolated, carbamate salts are easily formed in basic mixtures and ammonium carbamate is a commercial item. In the chemistry of amino acids, Frankel and Katchalski (Ref. 71) and, later, Bailey (Ref. 72) succeeded in isolating the "bimolecular" salts of N-carboxy-α-amino acid esters formed with the corresponding α-amino acid esters, i.e. organic ammonium salts of carbamic acids from the reaction mixture of various NCAs with alcohols :



It is well known that the stability (which is by no means the synonym of the inertness) of carbamate salts varies with the nature of the cation. The lower the acidity of the cation, the greater the stability of the salt. For example, the sodium salts of N-carboxy-α-amino acid esters are more stable than the above ammonium salts. On the other hand, the stability of carbamates for a given cation depends on the electronegativity of the substituents on the nitrogen atom. Thus, the higher the electronic density of nitrogen, the greater the stability of the carbamate. The "bimolecular" carbamate salt of sarcosine is more stable than that of glycine.

In the actual polymerization mixtures, carbamate group obligatorily appears with every reaction of polymerization (initiation or propagation), whichever is the mechanism that operates therein, and will be preserved when the conditions allow it, or will decarboxylate otherwise. When we want to discuss its fate, it is therefore important to bear in mind that carbamic acid is a real acid. In fact, the pK_a value of the carbamic acid on the growing chain end is not known, but it should not be far from 5.7, value cited by Shalitin (Ref. 73) for a known carbamic acid.

Thus, we are right to estimate that the concentration of carbamate is small because of the lack of the stabilizing counter-ion in the primary amine initiated polymerization, in which, after the rapid incorporation of the basic initiator in the very stage of initiation, the relatively electron-poor amino end group of the growing chain is the sole source of the basicity during all the propagation. Ballard and Bamford (Ref. 30) determined the equilibrium constants for the reaction of sarcosine derivatives and carbon dioxide and found values of 60 l^2/mol^2 (corresponding to about 8 % carbamate) for the "bimolecular" carbamate salt of sarcosine dimethylamide and 33.1 l^2/mol^2 (about 5 %) for that of sarcosine oligomer. The values for the N-unsubstituted amino acid derivatives are expected to be smaller. In the case of the tertiary amine catalyzed polymerization, the basic catalyst remains intact and the reaction mixture keeps its basicity. Trialkylamines have pK_b values usually between 3 and 4 in water, e.g. triethylamine giving 3.13 (Ref. 74), but they are probably more basic in organic solvents than in water (Ref. 75). The equilibrium constants should be higher than those given above, but still a major part of carbamate should decarboxylate.

This is not the case of the basic salt initiation using a strong base initiator, whose counter-ion ensures the stability of highly basic anions in the reaction mixture. Under these conditions, the resulting carbamate groups have no reason to decarboxylate systematically but will be preserved up to a certain concentration tolerated by the basicity of the mixture, which is near to the equimolecular concentration to the introduced basic initiator. It is not surprising that Seeney and Harwood (Ref. 63) found carbamate groups in the products of model reactions using very high concentrations of catalysts (monomer:

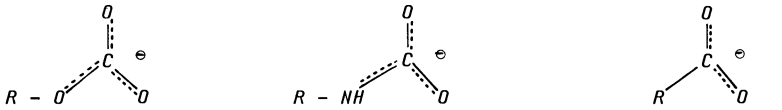
catalyst = 3 : 1 to 1 : 1).

2.2.5.2 Reactivity of carbamate group. Now that the presence of carbamate groups is admitted, the possibility of its reaction with NCA is to be examined. Some authors fear that carbamate does not react with NCA or that it is less nucleophilic than the amines from which it is derived. If it proved to be true, this would conflict with the fact of a faster polymerization by basic salts than by primary amines and negate Blout's mechanism.

Although no study of the model reaction using equimolar amounts of NCA and carbamate salt was not reported until now, fortunately some signs of the participation of carbamate in the polymerization are found in the literature. In the work cited above, Miwa and Stahmann (Ref. 60) demonstrated the initiating activity of benzoate anion, a carboxylate anion somehow analogous to carbamate, see reaction (ix). Shalitin (Ref. 76) proposed the new terminology of "acylate ion catalyzed polymerization" to cover the reactions promoted by carboxylate and carbamate salts. Giannakis and Harwood (Ref. 77) claimed the detection of initiation using solid sodium benzylcarbamate under aprotic conditions. Noting the importance of this problem, Goodman and Hutchison (Ref. 24, 43) studied the polymerization of γ-benzyl-L-glutamate NCA by use of C^{14}-labeled sodium benzylcarbamate and found "only 2.5 to 3.0 %" of incorporation. Unfortunately, their initiator was used in a "cold" methanol solution, condition allowing the initiation partly to arise from the action of sodium methoxide formed in an equilibrium (see Section 3), and, for the lack of data on the concentration, we cannot appreciate the value. We have simply to say here that, contrarily to the opinion of the authors, their results rather indicate the presence of a non-negligible fraction of chains initiated by the carbamate mechanism.

It is true that the amino group loses much of its nuclephilicity when it reacts with carbon dioxide (since this very reaction is a nucleophilic reaction) and, therefore, that the resulting carbamic group is much less nucleophilic than the mother amine. However, this does not imply anything about the nucleophilicity of carbamate anion, and still less about its reactivity in the NCA polymerization for the following reasons.

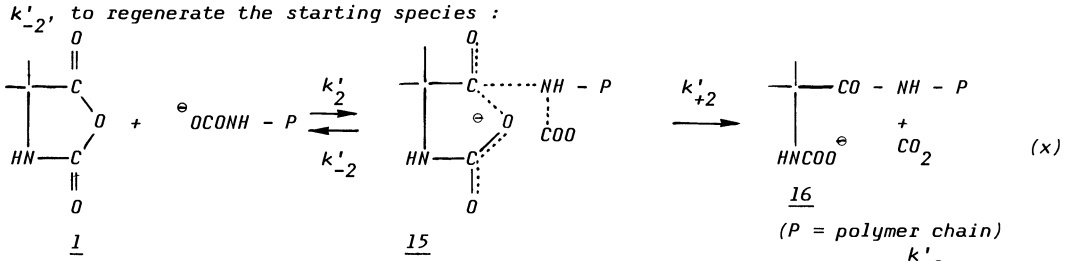
(1) The nucleophilicity of carbamate anion is the sum of the nucleophilicities of the two oxygen atoms and one nitrogen atom, the three being partially charged. In this respect, it is false to compare carbamate anion to carboxylate, as did Shalitin (Ref. 76); it should be compared to carbonate anion since the electronic structure of -NHR group resembles that of -OR, and since the charges, as well as the nucleophilic sites, are similarly distributed in R - NH - $CO_2^{\oplus}$ and R - O - $CO_2^{\ominus}$ anions.



carbonate anion | carbamate anion | carboxylate anion

Carbamate and carbonate anions are certainly less nucleophilic respectively than imino anion $^{\ominus}$NHR and alcoholate anion $^{\ominus}$OR, but not necessarily than the corresponding amine NH_2R and alcohol HOR.

(2) In every elementary reaction of propagation, the step of nucleophilic attack, k'_2, which is believed to be rate-determining (Ref. 69), is followed by another step, k'_{+2}, in which take place the charge neutralization, the rearrangement, the ring-opening and the gas release. However, a part of the reaction intermediate gives the reverse reaction k'_{-2}, to regenerate the starting species :

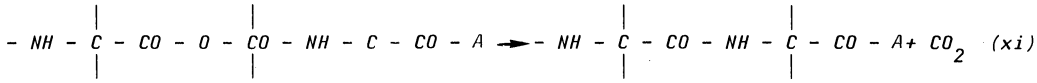


1 | 15 | 16 (P = polymer chain) (x)

The significance of the real reaction can be given by the product $k'_2 \times \frac{k'_{+2}}{k'_{+2} + k'_{-2}}$, in which k'_2 is a function of the intrinsic nucleophilicity of the attacking carbamete anion and the ratio $k'_{+2}/(k'_{+2} + k'_{-2})$ the probability with which the reaction intermediate 15 is converted into the reaction product 16 without being re-splitted into the starting products. This ratio normally depends on the electron density on the nitrogen atom, i.e. on the electron donating effect of its substituent groups. However, when carbon dioxide is released in gas form in the right reaction k'_{+2}, the ratio is near to unity. In this case, the reaction is pulled from the down-stream and becomes relatively significant even if the attacking

species is intrinsically not strongly nucleophilic, i.e. k'_2 only moderately great. Thus, carbamate anion appears to be highly reactive towards NCAs, while it is less reactive in the reactions which do not give the decarboxylation. In both cases, carboxylate anion with an equal basicity would be only moderately reactive, since no decarboxylation takes place.

2.2.5.3 Reaction intermediate. To account for the propagation by carbamate anion, Idelson and Blout (Ref. 16) assumed the formation of linear, mixed carboxylic carbamic anhydride, which would lose carbon dioxide by a spontaneous intramolecular rearrangement :

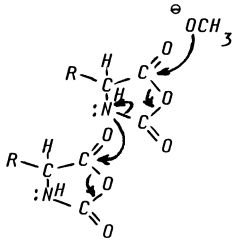


(xi)

17 18

Stressing the isocyanate character of NCAs, some authors (Ref. 40, 78) assumed the reaction of isocyanate group and carboxylic acid and they came across the same formula. The possibility of existence of such an anhydride was examined by Kopple and Thursack (Ref. 79) who gave a value of 0.24×10^{-4} s^{-1} for the decarboxylation of mixed ethylcarbamic phenylacetic anhydride into N-ethyl phenylacetamide. They concluded therefrom that the reaction is too slow to account for the observed rates of polymerization by the basic salt initiation. Later, Kricheldorf (Ref. 80), studying the synthesis of linear poly-N-carboxyamino carboxylic anhydrides corresponding to α, β, γ and ε-amino acids, obtained only the cyclic monomers for the two lower amino acids, whereas he succeeded in preparing the linear polymers of the two higher homologs. However, these polymers rapidly decarboxylated on addition of basic agent at 0°C. He concluded from it that the hypothesis of formation of linear N-carboxyanhydride group is not acceptable under the conditions of the base initiated polymerization.

An alternative mechanism conceived by Idelson and Blout (Ref. 16) assumes a direct attack of carbamate nitrogen and a simultaneous elimination of carbon dioxide through a series of purely electronic reactions. This mechanism was erroneously interpreted by Goodman and Arnon (Ref. 62) as an "amide anion" (or rather, imino anion) mechanism. The error was revived in some review articles, which unfortunately prevented this mechanism from being considered seriously. The arguments presented against the 'amide anion" mechanism, namely the non polymerization of methyl methacrylate in the presence of growing polypeptide chains (Ref. 62), are evidently irrelevant. In our opinion, this no-proton mechanism, which is just the schematic representation of reaction (x), accounts well for the low activation energy of 4 to 7 kJ/mol (Ref. 81, 82), and is chemically justified, although it seems to require slight modifications from the sterical point of view. A similar mechanism was suggested by Walker (Ref. 83) for the polymerization of sarcosine NCA.



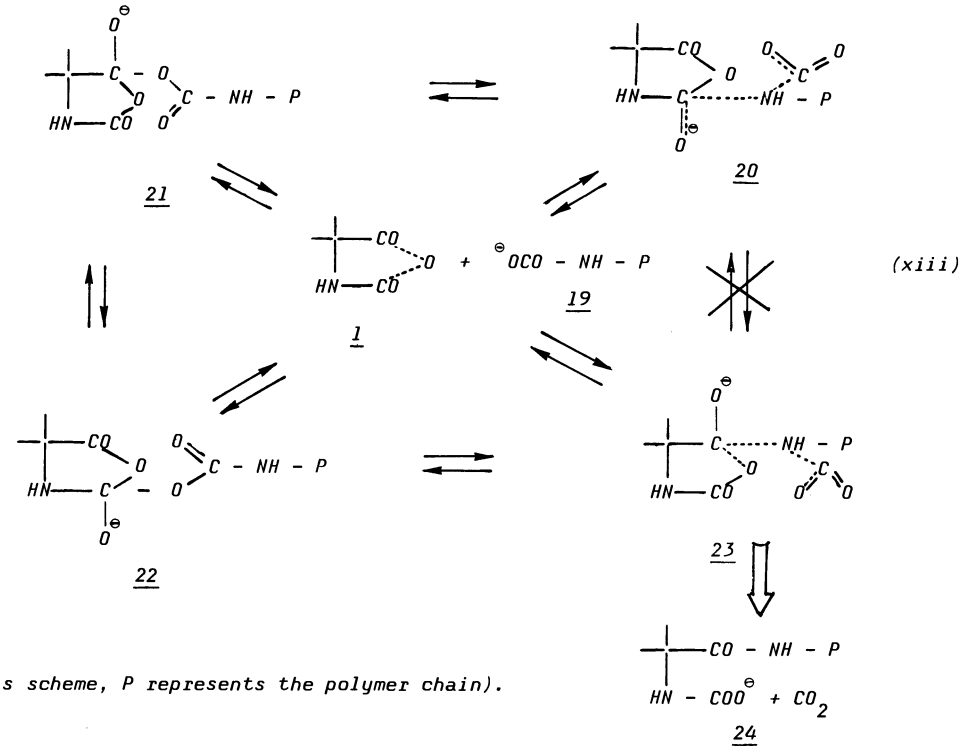
(xii)

The considerations given above lead us to the following mechanism. Carbamate anion in its oxanionic or nitranionic form reacts with NCA monomer on its 2-CO or 5-CO, giving four reaction intermediates 20 to 23, whose concentrations are strictly controled by the equilibria setting up between them. Among these four intermediates, only the one combining 5-CO and nitranion decarboxylates through a set of mesomerism, and is irreversibly transformed into the reaction product 24. The defect thus caused in the concentration of this intermediate is immediately filled by the displacement of the set of equilibria. According to this mechanism the attack of the initiator anion would be much less efficient than that of carbamate anion first, on account of the absence of carbon dioxide release, and second, for the lack of the equilibrium between the two possible reaction intermediates.
(See next page reaction (xiii)).

2.2.6 Kinetics and related problems

The kinetics theoretically expected for the reaction of polyaddition is very simple, if the reactions of termination are negligible as this is the case when high molecular weight polymers are obtained. Two cases are possible : (1) the rates of initiation k'_i and propagation k'_p are equal, (2) they are different. The first case corresponds to the "normal" polymerization mechanism and the second to the present one. The question was mathematiccaly treated by some authors (Ref. 42, 84). In these works, it is admitted that one nucleophilic initiator molecule or anion creates one polymer chain.

Experimentally, Idelson and Blout (Ref. 16) obtained a two stage kinetics, i.e a slow, long induction period followed by a rapid first order reaction, for the sodium methoxide initiated polymerization of γ-benzyl-L-glutamate NCA in dioxane (containing methanol). This appa-



(In this scheme, P represents the polymer chain).

rently seems to agree with the kinetics of slow initiation and rapid propagation, case (2). In fact, the results hide many details which prove the contrary. Blout and Karlson (Ref. 55) noticed that the $\overline{DP}$ of the resulting polymer was higher than that expected from the monomer/initiator ratio. Idelson and Blout (Ref. 16) found that only a small fraction of initiator is effectively utilized in the chain initiation (non quantitative conversion of the initiator), that the molecular weight of the polymer scarcely increases after 30 % conversion, while the kinetics was particularly of the first order in this part of the polymerization (reactions of chain transfer or permanent state of initiation and termination), and that the post-addition of monomer after the total conversion of the first fraction scarcely increases the final $\overline{DP}$ (chain transfer or desactivation of the polymer chains). Idelson and Blout (Ref. 16) tried to explain the problem of the non-quantitative conversion of the initiator by the reactions of termination. This problem was solved by Sekiguchi and Doussin (Ref. 17), who demonstrated the presence of an acid-basic equilibrium between the acidic NCA monomer and the basic salt initiator, by showing that the addition of the conjugate acid of the initiator accelerates the polymerization and increases the number of chains (See Section 4).

Analyzing the kinetics of the basic salt initiated polymerization of γ-benzyl-L-glutamate NCA of Idelson and Blout (Ref. 16), Peggion et al. (Ref. 28) indicated that the rate of reaction is proportional to $[I]^{0.5}$, $[I]$ being the initiator concentration. Moreover, Blout and Idelson (Ref. 85) reported that the time for 50 % conversion, $t_{0.5}$, and that for 90 % conversion, $t_{0.9}$, are proportional again to $[I]^{0.5}$, while Shalitin and Seltzer (Ref. 86) found that $t_{0.5}$ is proportional to $[M]_o^{0.5}$, $[M]_o$ being the initial monomer concentration. Adopting Blout's mechanism and assuming that the propagation constant is much greater than the initiation constant, $k'_p \gg k'_i$, Shalitin (Ref. 87) demonstrated that this mechanism agrees with these results. On the other hand, the theoretical molecular weight distribution of the polymer resulting from Blout's mechanism was derived by Katchalski et al. (Ref. 42) and by Ballard and Bamford (Ref. 30). It is broader than the Poissonian; the former authors gave $\overline{DP}_w/\overline{DP}_n = 1.33$. The value was verified by Yang (Ref. 88), Hall and Doty (Ref. 89) and later by Scoffone et al. (Ref. 90). It is noteworthy that all these results of kinetics and polydispersity in support of Blout's mechanism were obtained by the authors who use the sodium methoxide initiator in solution in a benzene/methanol mixture according to the recipe given by Berger, Sela and Katchalski (Ref. 54). This suggests that under certain conditions Blout's mechanism operates truly.

By the way, it would not be without interest to remark (Ref. 91) that the same kinetics could fit the "activated monomer" mechanism, admitting a kind of trimolecular reaction by the attack of the adduct of monomer and NCA anion by a second NCA anion in the initiation. On the other hand, Shalitin (Ref. 92) was somewhat perplex to find a k'_p/k'_i ratio of 1.5×10^4, too great to explain the difference of activity between methoxide anion and carbamate anion, although it would have been smaller if he had introduced an activity factor

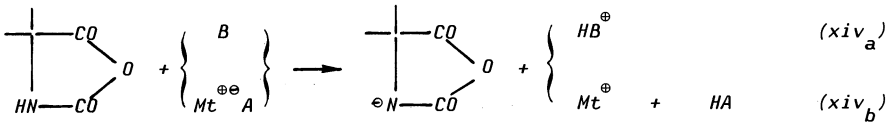
for the effective concentration of the initiator arising from the acid-basic equilibrium of Section 3. Anyway, this leaves a small possibility for the coexistence of the "activated monomer" mechanism in the above reactions.

2.3 "Activated Monomer" Mechanism

The mechanism was first conceived in 1956 by Ballard and Bamford (Ref. 12) for the tertiary amine catalyzed polymerization of DL-phenylalanine NCA and improved into the present form by Bamford and Block (Ref. 13, 14). Later, it was slightly modified by Szwarc (Ref. 93), who extended it to the basic salt initiated polymerization of N-unsubstituted NCAs. The arguments in support of the present mechanism are scarcely contested (see, however, ref. 63) as far as the tertiary amine and alkali halide catalyzed polymerization and the secondary amine initiated polymerization are concerned, in which the present mechanism is believed respectively to operate alone and to coexist with the "normal" polymerization mechanism. For the basic salt initiated polymerization, many experimental results agree well with the present mechanism, while they cannot be accounted for by the foregoing Blout's mechanism, but some others conflict with the former and seem to prefer the latter. Anyway, a moral support to the present mechanism is provided by the lactam salt catalyzed, anionic polymerization of lactams (Ref. 94 - 99), which is another example - and the only one existing at present - of the mechanisms of polymerization by the ionized monomer.

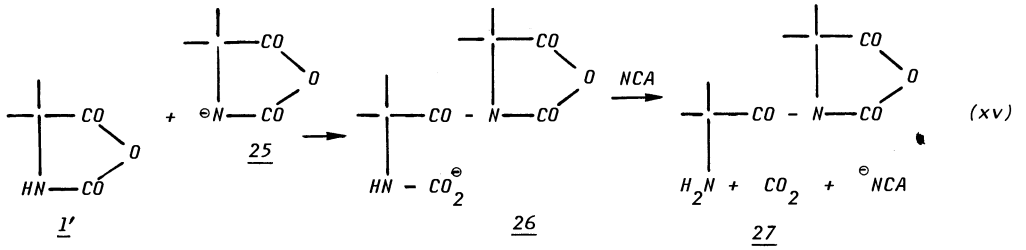
2.3.1 Reaction scheme

(1) Pre-initiation reaction : it is an acid-basic reaction between the acidic NCA monomer and the basic initiator. In this mechanism, the amine and basic salt initiators do not act as nucleophiles, but as bases in contrast to the "normal" polymerization mechanism and to Blout's mechanism, respectively. In other words, they are not chain initiators, but simply catalysts. Therefore, the monomer should obligatorily be N-unsubstituted (R^3 = H).



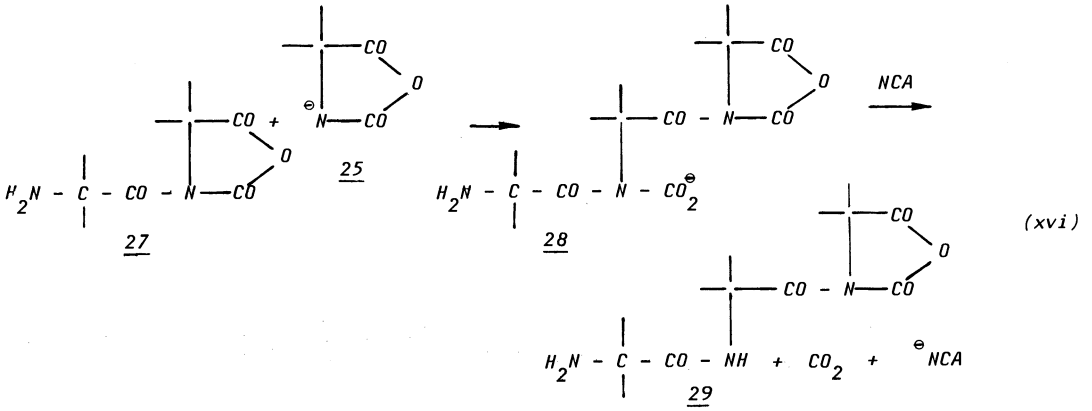
1 25

(2) Initiation : the resulting NCA anion acts as a nucleophile and attacks 5-CO of NCA monomer, giving a tadpole type dimer and releasing carbon dioxide. NCA anion is regenerated. The reaction is to be compared to the initiation through Blout's mechanism, reaction (vi), whose active species, the initiator anion, is here replaced by NCA anion.



1′ 25 26 27

(3) Propagation : the tadpole type dimer is attacked in turn by the same anion to give a tadpole type trimer, and so on. The chain growth takes place on the carbonyl side of the chain. NCA anion is regenerated in every elementary reaction.



27 25 28 29

2.3.2 Ionization of the monomer

2.3.2.1 Presence of NCA anion. The "activated monomer" mechanism assumes the role of the initiator as a base, hence the ionization of the monomer in an acid-basic reaction, to give NCA anion, which acts as an nucleophile. The ionization of the monomer is indispensible for this mechanism.

Sekiguchi et al. (Ref. 100, 101) determined the pK values of α-aminoisobutyric acid NCA and found 18.9 in 1,2-dimethoxyethane (DME) , in which methanol gives 24.0 ± 0.5 (Ref. 102). α-Aminoisobutyric acid NCA being one of the least acidic NCAs, other current NCAs can be considered to be in general more acidic than methanol. However, strictly speaking, the scales are not perfectly parallel for all variety of solvents and titration conditions.

It is true that NCAs range from weak to very weak acids and that, in the presence of moderately basic initiators such as triethylamine (pK_b 3.13, see ref. 74) they ionize only in very small concentrations. This led Kopple (Ref. 40) to consider that the "activated monomer" mechanism was unlikely. Bamford et al. (Ref. 103) replied to this criticism by saying that the weakness of an NCA as an acid implies that its anion is a strong base, and that, therefore, the latter adds rapidly to the 5-CO of NCA monomer of the growing chain. This is rather a curious reasoning, because, according to this interpretation, the lower the acidity of NCA, the greater its rate of polymerization would be. The true reason would be found in the equilibrium character of the reactions involved in the elementary reaction of propagation (paragraph 2.3.4).

A number of experimental results plead in favor of the hypothesis of ionization of NCAs. Thus, in diagnostic experimentents using pyridine, α-picoline and 2,6-lutidine as catalysts, Bamford and Block (Ref. 13) demonstrated that their activity, observed in the rate of polymerization, is in the order of base strength. Goodman and Arnon (Ref. 61, 62) reported the reaction of NCA with Grignard reagents such as methylmagnesium bromide in which the corresponding hydrocarbon gas (methane for the example) was liberated. In the same work, they noted that NCA decolorated immediately fluorenyllithium, though it could not be polymerized in this reaction. Further, Kricheldorf and Fehrle (Ref. 104, 105) succeeded in reacting 2-nitrophenylsulfenyl chloride with NCA in the presence of tertiary amine as the acceptor of hydrogen chloride and in obtaining the N-substituted derivative of NCA. The most convincing argument was presented by Choi and Goodman (Ref. 82) who isolated 6-oxo-L-pipecolic acid from the polymerization mixture of δ-benzyl-L-α-aminoadipate with sodium methoxide.

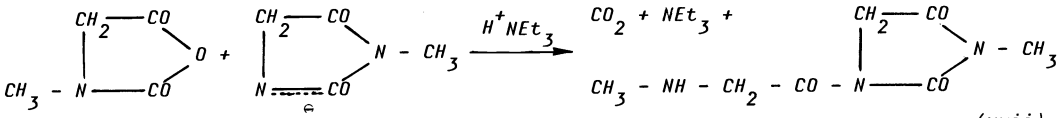
2.3.2.2 - Nucleophilicity of NCA anion . In the "activated monomer" mechanism the basic initiators do not act as chain initiators by their nucleophilicity, but only as catalysts by their basicity to produce NCA anion which, in turn, acts as the true nucleophilic agent of the polymerization. In this case, the polymer chain is self-initiated.

The above cited works of Kricheldorf and Fehrle (Ref. 104, 105) on the synthesis of N-(nitrophenylsulfenyl) NCA provided an example of the reactions making use of the nucleophilicity of NCAs. Otherwise, the initiating power of NCA anion is generally more evidenced by the absence of the initiator used or its fragment than the presence of the amino end group in the resulting polymer. Thus, many authors (Ref. 23, 24, 106, 107) proved that the polymers from the secondary or tertiary amine catalyzed polymerization were free from the initiator residue.

The problem of the incorporation or non-incorporation of the initiator moiety for the basic salt initiation was debated in paragraph 2.2.3.1. Apparently the opinions are divided.

2.3.2.3. Infeasibility of the mechanism for N-substituted NCAs . In spite of the title, many authors polymerized N-substituted NCAs (R3 ≠ H), in particular sarcosine and proline NCAs (Ref. 24, 31, 61, 62, 108, 109), (S)-thiazolidine-4-carboxylic acid NCA (Ref. 110) and sarcosine NTA (N-thiocarboxyanhydride, Ref. 109) by the action of tertiary amines or in pyridinic solvents. For Bamford's team (Ref. 31, 70, 108), however, the polymerization of these NCAs by aprotic initiators is intrinsically impossible and all the positive results in the literature are the fact of the reaction of the impurities or the proton on 4-position of the monomer. Ballard and Bamford here mean by impurities the protic impurities (HX) ionizable in the presence of the basic initiator. According to them, such impurities serve as the source of proton and, when they are present at the same time as the basic initiator, their anions initiate the polymerization by being incorporated in the resulting open-chain (carbamic acid) unit, which then decarboxylates. After that, the propagation takes place by the "normal" polymerization mechanism on the free amino end group thus created. They showed ingeniously the necessity to have a source of proton in the initiation by use of tertiary amines or alkali halides. Thus, sarcosine NCA was nearly inactive in the presence of the initiator alone, but it polymerized rapidly when a small amount of 3-methylhydantoin was added. They explained the phenomenon by the ionization of 3-methylhydantoin and the addition of the resulting anion 30 on 5-CO of NCA monomer, to give rise to a kind of dimer or, more exactly, a heterodimer, carrying a secondary amino end group, 31, which would now propagate by the "normal" polymerization mechanism, reaction (iv). The idea

is good, because the proposed mechanism, which is based on the hypothesis of ionization of this model compound (3-methylhydantoin), accounts first for the polymerization of the non-ionizable NCAs, and this in turn proves the validity of the hypothesis, and consequently the ionization of N-unsubstituted NCAs. The proposed mechanism is as follows :



1' 30 31 (xvii)

In a later work, Bamford and Block (Ref. 70) extended this mechanism to the basic salt initiated polymerization, by adopting the hypothesis of deprotonation on 4-position of N-substituted NCAs and assuming the initiation by the resulting carbanion.

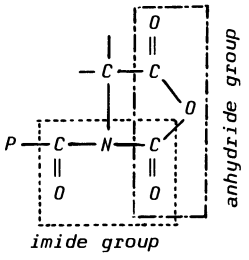
The inspection of their roundabout mechanism leads us to formulate some remarks. First, it is true that the polymerization is much accelerated by the addition of protic compounds. The mechanism of the induced initiation is good (we have reserves about the propagation). However, this does not mean that the slow, persisting polymerization of N-substituted NCAs is also due to protic impurities. Second, since the mechanism of the induced initiation is good, it should hold for a variety of ionizable impurities or protic additives, in particular water and alcohols. Ballard and Bamford (Ref. 108) pointed out the accelerating effect of water on such a polymerization. The result could not be explained, if the initiating power were not acknowledged for hydroxyl and alcoholate anions. In other words, Ballard and Bamford contradict with themselves because, meaning to avoid Blout's mechanism, they proposed another one which, without their knowing it, includes this mechanism as an example. Third, the deprotonation on 4-position will surely take place to a certain extent in the presence of basic agents, but the participation of the resulting carbanion in the polymerization should be much smaller than that of alcoholate anion, since the latter is enough nucleophilic and exists in a much higher concentration than the former. Fourth, there is no reason that carbamate group disappears from the chain end during the propagation, at least as far as the basic salt initiated polymerization is concerned.

Bamford and Block are not alone to adopt the hypothesis of deprotonation on 4-position. Originally presented by Goodman and Arnon (Ref. 62) for the initiation by use of basic salt initiators and then abandoned (Ref. 24), this hypothesis was recently revived by Kricheldorf (Ref. 109) for the polymerization of sarcosine NCA and proline NCA by triethylamine. The same author proposed a zwitter-ion mechanism, somewhat different from that once suggested by Wieland (Ref. 111) in that it involves a betain type intermediate, for the pyridine initiated polymerization of the same N-substituted NCAs. Indeed, it is possible that the initiation by NCA carbanion comes to the surface when other less basic initiating anion, i.e. normally more easy to form, is absent. For these two reactions, Kricheldorf assumed the participation of carbamate anion in the propagation.

The problem of the basic salt initiated polymerization of N-substituted NCAs was debated in paragraph 2.2.3.2.. The majority of results seem to be consistent with Blout's mechanism in this case.

2.3.3 Electrophilicity of N-acylated NCA unit

The "activated monomer" mechanism is characterized by the formation of a new electrophilic species on the chain end : N-acylated NCA unit. It is a kind of mixed anhydride of carboxylic acid and (hypothetical) "imidoic" or "carbimidic" acid, that possesses a series of polar groups in which acid anhydride group and imide group are fused (Ref. 101, 112). The presence of such a group at the chain end was experimentally shown by Terbojevich et al. (Ref. 107). This part of the chain is believed to be more electrophilic than the monomer and to compete with it in the reaction with NCA anion. The situation resembles that of the anionic polymerization of lactams (cyclic amide compounds), in which is formed a N-acylated lactam end unit carrying an imide group (Ref. 94-97). This species is much more reactive than the lactam monomer and receives the attack of lactam anion in the reaction of propagation. The resemblance is normal, since NCAs are a kind of lactams. Yet, a small difference exists between the two polymerizations : while lactams often require the addition of N-acylated lactam or other imidic compounds, besides the anionic catalyst, to initiate the polymerization at relatively low temperatures, NCAs are usually electrophilic enough to give alone the reaction of initiation (self-initiation) in the presence of basic catalyst without a chain initiator (N-acylated NCA) being added.



32 (xviii)

However, the high electrophilicity of NCAs does not prevent us from observing the effect of addition of the chain initiators of the type N-acylated NCA. When prepared *extra situ* and introduced at the time of initiation they allow to skip the stage of initiation reaction, to give directly the propagation on their own molecules. The best example is given by N-acetylglycine NCA, prototype of the growing chain, first prepared by Dyer et al. (Ref. 113) and later by Kricheldorf (Ref. 114). The latter author used the compound in the tertiary amine catalyzed polymerization of glycine NCA, to demonstrate the incorporation of the acetyl group in the resulting oligopeptides, to the advantage of the "activated monomer" mechanism. Using α-aminoisobutyric acid NCA, monomer whose electrophilicity is relatively low, Sekiguchi and Froyer (101) observed a significant acceleration of the tertiary amine catalyzed polymerization even in the presence of 1-acetyl 3-methylhydantoin and 1-acetyl 2-pyrrolidone, model compounds of N-acylated NCA but having a lower electrophilicity than N-acetylglycine NCA.

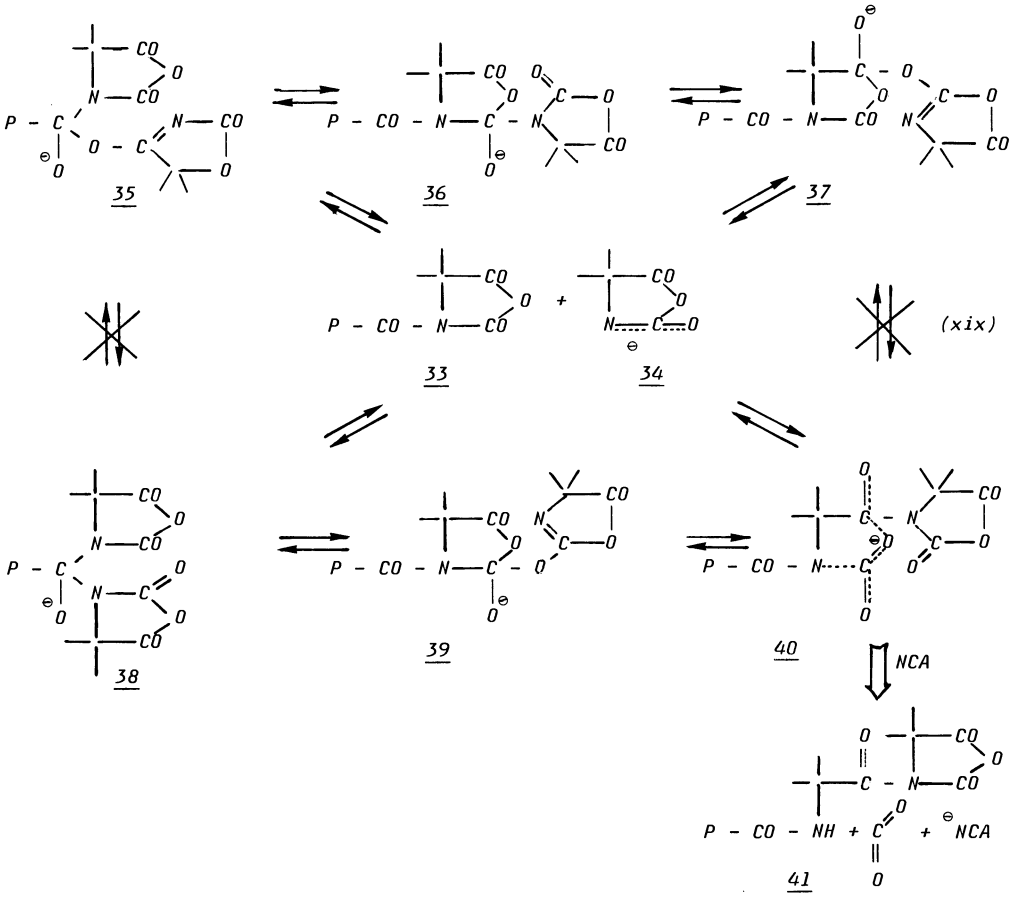
For the basic salt initiated polymerization, Ruderman-Amouyal, Coutin and Sekiguchi (Ref. 115) found a similar effect of acceleration by the addition of N-acetylglycine NCA. This is evidently a support to the "activated monomer" mechanism, though, strictly speaking, it does not prove the mechanism. Curiously, the sodium methoxide initiated polymerization of α-aminoisobutyric acid NCA was still more accelerated when methanol was added at the same time as N-acetylglycine NCA. The fact suggests on the one hand that, if the "activated monomer" mechanism actually operates in this polymerization, the N-acetylated NCA end unit of the growing chain resists at least for a while to the attack of methanol or methoxide anion, and on the other hand that, under these conditions, the polymerization involves at the same time the "activated monomer" mechanism and another mechanism susceptible to the acceleration by methanol, Blout's mechanism in this case. In a study relating to this problem, Ruderman and Sekiguchi (Ref. 116) polymerized α-aminoisobutyric acid NCA by the sodium methoxide initiation in the presence of several model compounds, namely 1-acetyl 3-methylhydantoin, 3-acetyl 2-oxazolidone and 1-acetyl 2-pyrrolidone, to compare them to N-acetylglycine NCA. In contrast to the last compound which clearly presented the expected accelerating effect, the first two compounds exhibited a rather depression effect, while 1-acetyl 2-pyrrolidone remained practically inert. These results can be reasonably interpreted when the simultaneous presence of two opposite effects of acceleration and depression for each additive are assumed as follows. The acceleration effect is the measure of the ease with which the N-acylated derivative is converted into N-acylated NCA (the true chain initiator) by the reaction with NCA anion, *i.e.* the significance of its reaction of acyl exchange with NCA anion. Obviously, N-acetylglycine NCA comes to the top of the order, since it does not require any reaction of the kind. The depression effect is the measure of the ease with which the additive reacts with the coexisting methoxide anion of Blout's mechanism without giving the chain initiation, *i.e.* acyl exchange with methoxide anion. This reaction, which yields methyl acetate, consumes the initiator anion. Except N-acetylglycine NCA, with which the chain initiation is direct and instantaneous, the other N-acylated derivatives seem to be more "efficient" in depression than in acceleration (see discussion in Section 4).

2.3.4 Reaction intermediates

The high rate of polymerization in the "activated monomer" mechanism is generally attributed to the high electrophilicity of the N-acylated NCA unit. It may be true at least for the tertiary amine catalyzed polymerization. However, a high electrophilicity supposes a high reactivity as well with NCA anion as with any other anion. At the first sight it is difficult to explain the apparently high reactivity of this end unit towards NCA anion and a low reactivity towards the initiator anion in the sodium methoxide initiated polymerization, since there is no reason for the former to be much more nucleophilic than the latter.

The results can be explained when we assume that both of them are rather weakly nucleophilic in nature, but that the reaction of propagation is drawn from the down-stream by the departure of carbon dioxide gas, which "pumps" the equilibrium of reaction intermediates in the sense of the right reaction while such an equilibrium does not exist for the reaction intermediates of attack of the initiator anion. Sekiguchi and Froyer (Ref. 101) assumed that all the three carbonyl groups of the N-acylated NCA end unit are more or less polarized and susceptible to the attack of NCA anion under both nitranion and oxanion forms, giving in total six reaction intermediates which belong to two groups of interconversion (see reaction (xix)). They are on the one hand the reaction intermediates resulting from the attack of exo-CO by nitranion, **38**, the attack of 2-CO by oxanion, **39**, and the attack of 5-CO again by nitranion, **40**, and on the other hand those resulting from the attacks of the same carbonyl groups by the opposite anions, respectively **35**, **36** and **37**. The criticism formulated by Kricheldorf (Ref. 114) on this subject (inertness of 5-CO and exo-CO towards the attacks of NCA anion) falls aside, since it is here the question of the formation of the reaction intermediates, while he dealt with the final reaction products. Among these six reaction intermediates, only the one combining 5-CO and nitranion, **40**, releases carbon dioxide through a series of mesomerism and is definitively converted into the reaction product. The defect thus caused in the concentration of this intermediate is then filled by the displacement of the set of equilibria. The reaction intermediates **35** to **37** cannot give any real reaction, because none of them decarboxylates. When the attacking anion is metho-

xide anion, no equilibrium of interconversion sets up between the three intermediates of the types 35, 37 and 39. Only the intermediate from 5-CO and the initiator anion (intermediate type 37) leads to the termination. This mechanism agrees with the low activation energy of 4 to 7 kJ/mol (Ref. 81, 82), as does the mechanism (xiii).



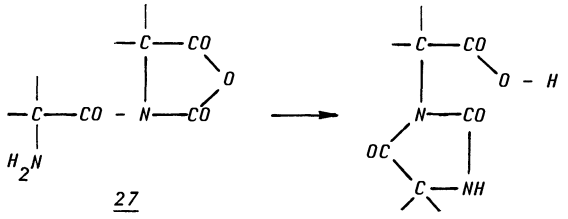
2.3.5 Other aspects of the polymerization

2.3.5.1 Kinetics . The "activated monomer" mechanism is expected to present a greater rate of polymerization than the "normal" polymerization mechanism. In particular, the reaction of propagation with this mechanism should be faster than that of initiation, contrarily to the latter mechanism. These characteristics were verified by Peggion et al. (Ref. 28) who pointed out the resemblance of the kinetics of polymerizations initiated by di-n-butylamine or diisopropylamine and by sodium methoxide. However, Shalitin (Ref. 86), who examined the kinetics of polymerization by the latter initiator, had to conclude rather to Blout's mechanism than to the present, in spite of some elements which pointed to the contrary (see paragraph 2.2.6). No similar work was attempted on the tertiary amine catalyzed polymerization because its kinetics is usually disturbed by side reactions.

2.3.5.2 3-Hydantoin-acetic acid type by-products. Ballard, Bamford and Weymouth (Ref. 117) reported the detection of 3-hydantoin-acetic acid type by-products in the alkali halide and tertiary amine catalyzed polymerizations of various NCAs. No piperazine-2,5-dione derivatives were formed. The resulting polymer presented an average molecular weight much greater than expected from the starting monomer/initiator ratio and displayed a very wide distribution of molecular weights. These results as a whole are consistent with the "activated monomer" mechanism.

Besides the reactions catalyzed by alkali halides and tertiary amines, some particular polymerizations are cited in the literature as providing 3-hydantoin-acetic acid type by-products. They are the strong (in fact, weak) base initiated polymerization of γ-benzyl-L-glutamate NCA (Ref. 118) and the sodium methoxide initiated polymerization of α-aminoisobutyric acid NCA (Ref. 115). Seeney and Harwood (Ref. 61) remarked that in the primary, secondary and tertiary amine initiated polymerizations of L-phenylalanine NCA large amounts of 3-hydantoin-acetic acid derivative (and even piperazine-2,5-dione derivative) were formed when the released carbon dioxide was immediately swept off from the reaction mixture. It is interesting to note that all these polymerizations are relatively slow, either because of

the weak basicity of the catalysts, or the weak acidity of the monomer, or on account of the environmental conditions (dilution, insufficiency of catalysts, etc.).



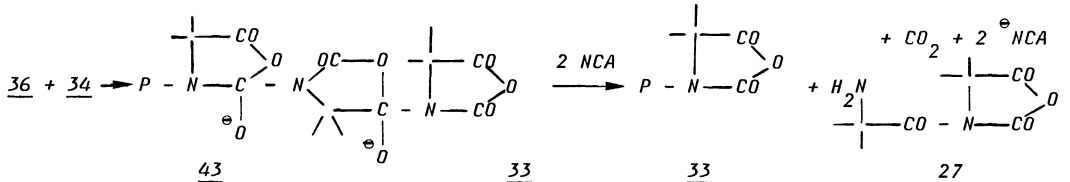
27 42 (xx)

The formation of 3-hydantoin-acetic acid derivatives is a strong support to the "activated monomer" mechanism (Ref. 115), since reaction (xx) requires the presence of the tadpole type dimer 27 in the polymerization mixture. Thus, when the bimolecular reaction of propagation, reaction (xvi), is slow, the tadpole type dimer 27 has the time to give the monomolecular reaction of cyclization, theoretically slow on account of the anionoid character of the reaction. This reaction seems to be generally favored by the decarboxylation of carbamate group, which means that it is easier for the free amino end group than for the carbamate group, although it is significant enough even with the latter group when the lowly polymerizable α-aminoisobutyric acid NCA is polymerized by the sodium methoxide initiation.

Two interpretations are possible in principle to explain the fact that 3-hydantoin-acetic acid type by-products are not formed in the sodium methoxide initiated polymerization of current amino acid NCAs (Ref. 119) : (1) the sodium methoxide initiated polymerization proceeds by the same mechanism as the tertiary amine catalyzed polymerization, but the reaction conditions do not allow the side reactions of this kind (e.g. the polymerization is very fast), (2) it proceeds by another mechanism, Blout's one in this case, which cannot involve this type of side reactions. We are attempted to adopt the hypothesis (1), since α-aminoisobutyric acid NCA, poorly acidic and lowly ionizable monomer, polymerizes yet through the "activated monomer" mechanism, as the significant amount of 3-(5.5-dimethylhydantoin)-isobutyric acid formed proves it (Ref. 115). Studying this polymerization, Ruderman-Amouyal, Coutin and Sekiguchi found that, when a certain amount of methanol is added to the reaction mixture, the yield in the hydantoin type by-product falls to zero, whereas the polymerization is accelerated (in fact, the number of chains increases). They concluded therefore that the mechanism changes from the one by the "activated monomer" to Blout's one when methanol is added.

2.3.5.3 Reactions of termination. The comparison of the sodium methoxide initiated polymerization described by Blout and his coworkers in their earlier works (Ref. 16, 55) to the alkali halide and tertiary amine catalyzed polymerization reported by Ballard, Bamford and Weymouth (Ref. 12, 31) reveals two interesting features of the aprotic base initiated polymerizations : (1) their resemblance as exemplified by the formation of a small number of long chains, and (2) their dissimilarity as shown by the distribution of molecular weights of the resulting polymers.

The wideness of the distribution of molecular weights found for the polymers from the tertiary amine catalyzed polymerization (Ref. 12) is probably due to the formation of 3-hydantoin-acetic acid (see paragraph 2.3.5.2) and cyclic oligomers (see paragraph 2.3.5.4), but the hypothesis of the presence of the reaction of chain transfer is not excluded. The mechanism of the latter reaction has remained unknown for a long time. In a work dealing with the anionic polymerization of lowly polymerizable C-substituted 2-pyrrolidones, Deratani and Sekiguchi (Ref. 120) assumed that the anionic intermediate of propagation is attacked by a second lactam anion when the chain growth becomes slow (for example in consequence to the occlusion of the growing chain end in the precipitated polymer). Froyer (Ref. 121) assumed a similar reaction taking place, certainly with a weak probability, on the reaction intermediates of wrong attacks. It reminds us of the hypothetical trimolecular mechanism of initiation suggested in paragraph 2.2.6. Without giving the detail, Szwarc (Ref. 122) admitted the possibility "that the termination, or chain transfer, involves some reactions which are of second (or still higher) order in initiator".



36 + 34 → 43 33 2 NCA 33 + CO2 + 2 ⊖NCA 27 (xxi)

2.3.5.4 Bifunctionality of the resulting polymer. The polymer chain from the polymerization through the "activated monomer" mechanism should be bifunctional with a nucleophilic free amino group on the one end (see paragraph 2.1.2) and the electrophilic N-acylated NCA unit on the other (see paragraph 2.3.3). Consequently, they should react intramolecularly when sterically possible, or intermolecularly when their concentration is high. The formation of 3-hydantoin-acetic acid derivatives by the cyclization of the tadpole type dimer 27, discussed in paragraph 2.3.5.2 is just a consequence of the bifunctionality at the level of the dimer. Similar reactions of higher oligomers, now by the attack of 5-CO in the absence of the steric hindrance, lead to the formation of cyclic oligomers as this was shown by Bamford's team (Ref. 117, 123) and Rothe et al. (Ref. 124). The bifunctionality was further demonstrated by the Italian school (Ref. 106, 125) that showed that the reaction of post-polycondensation of the polymer chains actually takes place upon the concentration of the reaction mixture arising from a strong base initiated polymerization. Peggion et al. (Ref. 106) indicated, moreover, that the polymer before as well as after the post-polycondensation presents a molecular weight distribution corresponding to the "most probable distribution of polycondensates."

3. COEXISTENCE OF THE THREE MECHANISMS

We have shown above that all three classical mechanisms operate in the base initiated polymerization of NCAs according principally to the nature of the initiator used and accessorily to the reaction conditions, and that very few examples of the actual polymerizations involve purely one of them to the exclusion of the others. Thus, we are led to admit, in the following part of the discussion, the presence of some equilibrium reactions which would strictly control the concentration of the specific active species of each mechanism. After that, we assume the chain initiation by all the nucleophilic species implicated in them, followed by the reactions of chain growth whose significance will be now regulated by a new equilibrium setting up between the ionic species of these reactions. We will thus draw up a list of the principal reactions possibly taking place in the reaction mixture.

3.1 Acid-Basic Equilibrium in the Pre-Initiation Stage

Our hypothesis of coexistence of three mechanisms is based on an acid-basic equilibrium (very fast reaction) setting up between the acidic NCA monomer and the basic initiator. According to the nature of the initiator used, two reactions are possible :

$$NCA + B \underset{k_{-o}}{\overset{k_{+o}}{\rightleftharpoons}} NCA^{\ominus}\ {}^{\oplus}BH \qquad (xxii_a)$$

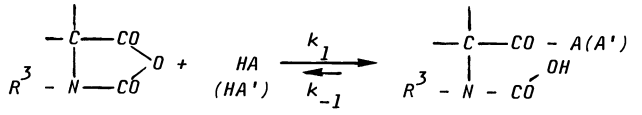
$$NCA + Mt^{\oplus}\ {}^{\ominus}A \underset{k'_{-o}}{\overset{k'_{+o}}{\rightleftharpoons}} NCA^{\ominus}\ {}^{\oplus}Mt + HA \qquad (xxii_b)$$

Thus, the reaction mixture contains normally, besides NCA monomer, two (the basic initiator and NCA salt) or three (the basic initiator, NCA salt and the conjugate acid of the initiator) species. We assume that all these species independently participate in the nucleophilic reactions of chain initiation (less fast reactions), either directly when they are nucleophilic agents, or by their anionic moieties when they are in ionic form. It is to be noted that equilibrium ($xxii_b$) is known in the classical mechanisms, but it is completely shifted to the right in the "activated monomer" mechanism and, so to speak, to the left in Blout's mechanism.

3.2 Reactions of Chain Initiation

3.2.1. Chain initiation by the protic base

The protic bases, B (when B = HA') of equilibrium ($xxii_a$) or HA of equilibrium ($xxii_b$), which contain a removable proton bound to a basic heteroatom, act as chain initiators. The reversibility of the reaction will depend on the electron-withdrawing effect of A or A' group in the reaction product. The reaction corresponds to the initiation by the earlier "normal" polymerization mechanism, but we prefer to specify the attacking species and to call it the chain initiation by the protic base. The decarboxylation or no decarboxylation of the resulting chain will be discussed in paragraph 3.3.1. Evidently, this reaction is absent when B is an aprotic base (tertiary amine).

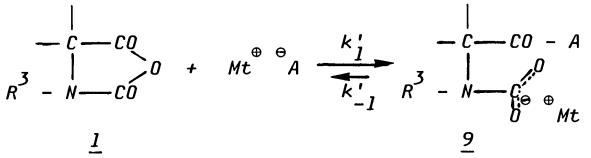


(xxiii)

1 44

3.2.2 Chain initiation by the initiator anion

Since amines and other protic bases usually do not ionize alone, this mechanism does not regard the polymerization by their use. It is the part of basic salt initiator $Mt^{\oplus}\,{}^{\ominus}A$, not transformed by equilibrium (xxii$_b$), that is here concerned. The anionic moiety ${}^{\ominus}A$ is a nucleophilic agent and acts as a chain initiator. The reaction is reversible when group A in the resulting open-chain unit is highly electron-withdrawing. The preservation of carbamate group will be discussed in paragraph 3.3. This reaction corresponds to the initiation by the former Blout's mechanism, but we prefer to call it by the name of the anion.

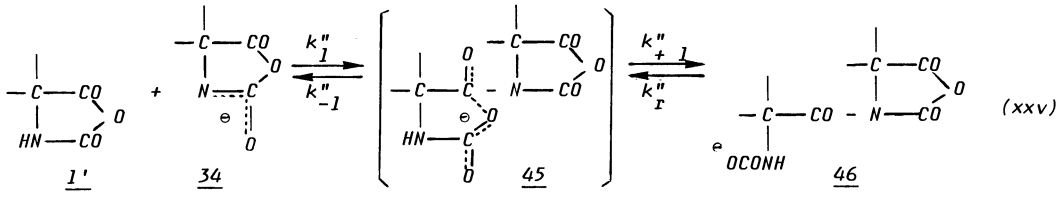


(xxiv)

1 *9*

3.2.3 Chain initiation by NCA anion

NCA salt, formed in equilibrium (xxii$_a$) or (xxii$_b$) is at the origin of this mechanism. NCA anion 25 is the nucleophilic agent of the reaction and acts as a chain initiator. The reaction is reversible because of the relatively high electron-withdrawing effect of the NCA ring unit in the tadpole type dimer 46, which possesses a very highly electrophilic, mixed anhydride group on the one end and a nucleophilic carbamate anion on the other. The decarboxylation or non-decarboxylation of this carbamate group will be discussed together with that of the carbamate groups of other origins. The reaction corresponds to the initiation by the former "activated monomer" mechanism; we propose to call it by the name of the anion.



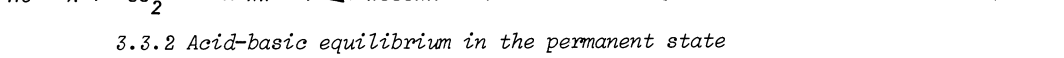
(xxv)

1' *34* *45* *46*

3.3. Post-Initiation Equilibria

3.3.1 Equilibrium of carboxylation and decarboxylation

The concentration of carbamate group in the reaction mixture does not depend on the mechanism of chain initiation. All the mechanisms of initiation mentioned above provide either carbamic acid or carbamate end groups, which are interconvertible within the limit of the concentration in carbamate which varies with the basicity of the reaction mixture. It is to be noted that it is here the question of the acidity or the basicity of the species present, and not the species introduced, since certain initiators disappear by their incorporation into the resulting polymer at the stage of initiation. Beneath the upper limit of the concentration of carbamate thus defined, equilibrium (xxvi) of carboxylation and decarboxylation sets up in which HX represents all the coexisting acids, weak and very weak, including NCA monomer. The constant of equilibrium is a function of the basicity of the mother amine or electron density of its nitrogen atom, which depends on the nature of the substituents, R^3 and P. Thus, for a given counter-ion, carbamate group is formed in higher concentration with polysarcosine than polyglycine. The surplus part of carbamic acid or carbamate, formed by whichever mechanism it may be, decarboxylates to give free amino end group. In other words, the mechanism of initiation does not predestinate the resulting carbamate group to the preservation or the decomposition.

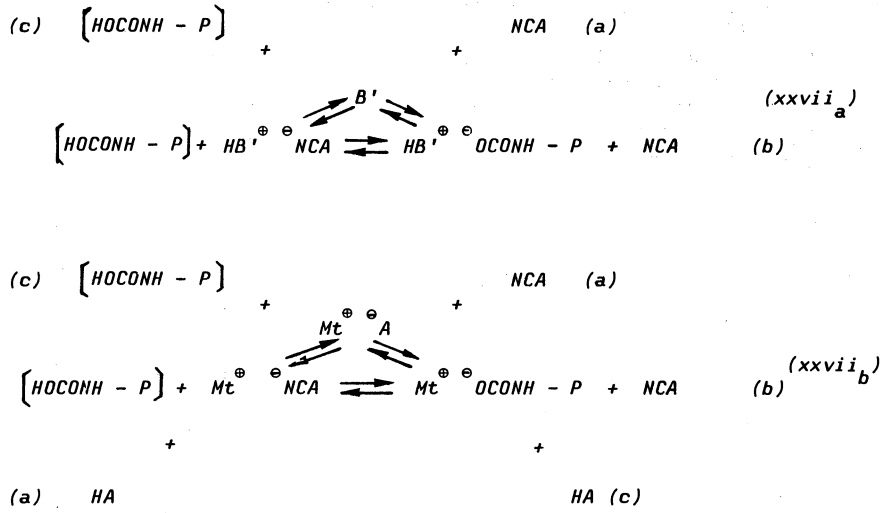


(xxvi)

3.3.2 Acid-basic equilibrium in the permanent state

When carbamate group is formed in consequence of the reaction of initiation, the basicity of the reaction mixture decreases. On the other hand, a part of initiator or of its anion disappears at the stage of initiation and amino end group appears if a part of carbamate decarboxylates. These changes modify the balance of power between the active species and transform the initial acid-basic equilibria, reactions (xxii$_a$) and (xxii$_b$), respectively into reactions (xxvii$_a$) and (xxvii$_b$), in which B' represents the sum of the remainder of non-ionic initiator and the newly formed amino end group. It is important to note that equilibrium (xxvii$_a$) is present in all the polymerizations involving the decarboxylation of carbamate end group, irrespectively of the presence or absence of equilibrium (xxvii$_b$). When $Mt^{\oplus}\,{}^{\ominus}A$ tends to be eclipsed by the two other salts, equilibrium (xxvii$_b$) is reduced

to equilibrium (xxvii$_b$ - (b)), while, when HB'$^{\oplus}$ $^{\ominus}$OCONH - P does not increase much, equilibrium (xxvii$_b$) can be approximated by equilibrium (xxvii$_a$ -(a)), i.e. (xxii$_a$). The chain initiation in the later phase of the polymerization will be given by the initiating species implicated in these new equilibria.

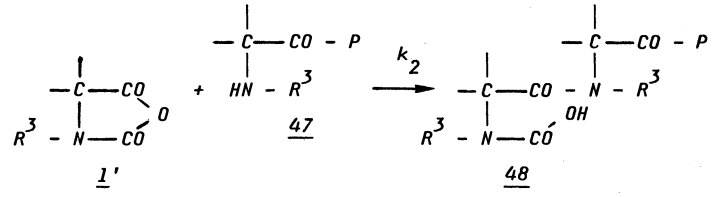


3.4 Reactions of Chain Growth

The chains resulting from the above reactions of equilibrium grow through their proper mechanisms by amino end group or by carbamate anion irrespectively of the mechanism of their formation, i.e. the initiation. On the contrary, chain growth by reaction with NCA anion requires chain initiation by the same anion.

3.4.1 Aminolytic mechanism

This mode of chain growth is given by the growing chain carrying a free amino end group; it is present when the reaction mixture is only weakly basic. The amino group reacts with NCA monomer to give reaction (xxviii). The reaction is practically irreversible, because the nitrogen atom of the penultimate monomer unit in the resulting chain is very lowly electron-withdrawing, which means that its peptide bond is solid. Whether the resulting carbamate group decarboxylates or not does not depend on the mechanism of chain growth, but only on the equilibrium of carboxylation and decarboxylation of the moment. We propose to avoid the ambigous name of "normal" polymerization mechanism and to call it the <u>aminolytic (polymerization) mechanism</u> for this part of the reaction (chain growth).



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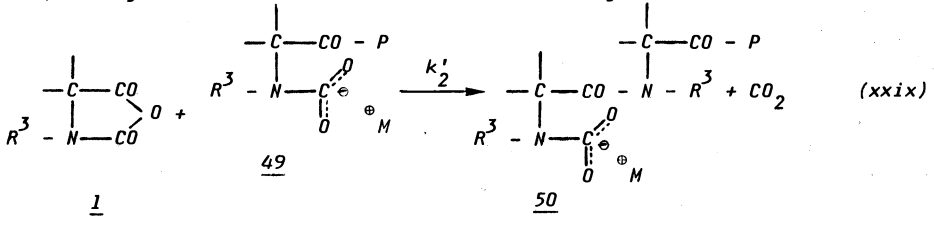
3.4.2 Carbamate anion mechanism

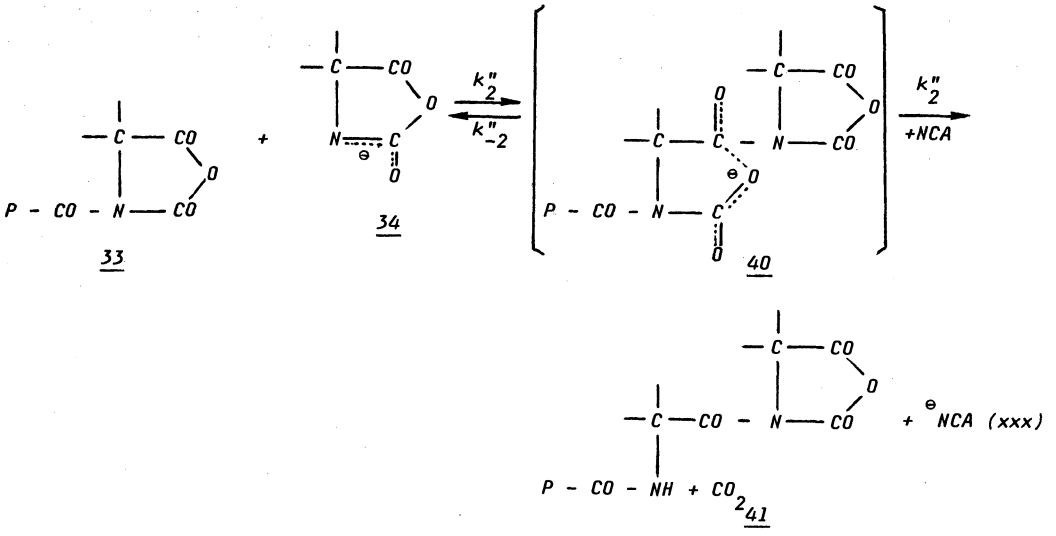
The initiation by the initiator anion, reaction (xxiv), is not the prerequisite for the present mode of chain growth since carbamate group is present in more or less important concentration in any base initiated polymerization. It gives a nucleophilic attack on NCA monomer and is decarboxylated to give a newly formed carbamate group. Similarly to those formed in the reactions of initiation, the resulting carbamate group participates in the equilibrium of carboxylation and decarboxylation. This mechanism corresponds in the main to Blout's mechanism, but we propose to call it the <u>carbamate anion mechanism</u> for this part of the reaction (chain growth) to contrast with the mechanism by NCA anion.



(xxix)

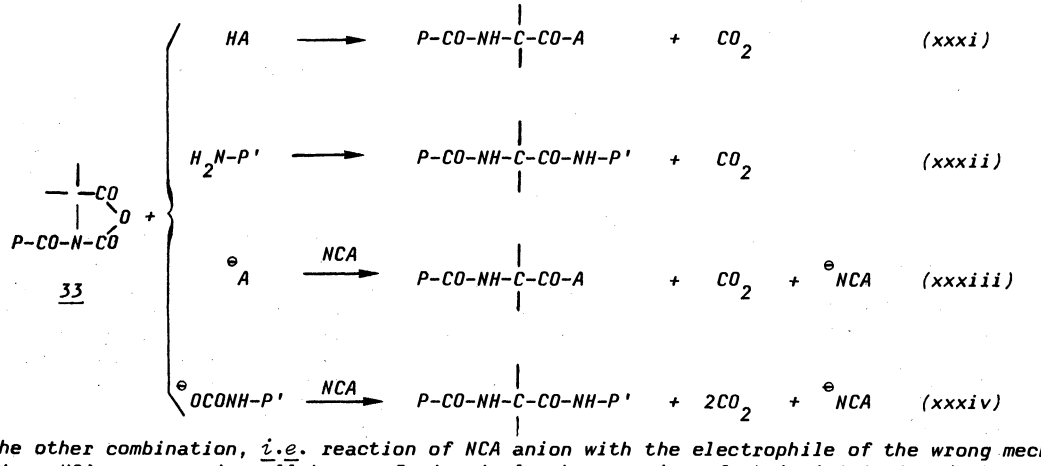
3.4.3 NCA anion mechanism

NCA anion is present in all polymerization mixtures using basic initiators. This mechanism is characterized by the fact that it requires the chain initiation by the same anion (see paragraph 3.2.3), in contrast to the two other mechanisms which have no prerequisite for the mode of initiation. The chain growth proceeds by the nucleophilic attack of NCA anion on the N-acylated NCA end unit of the growing chain, followed by the decarboxylation of the latter into an amide (peptide) group. Since this group is lowly nucleophilic and cannot be carboxylated into a carbamate-like anion, the reaction is essentially irreversible in contrast to the chain initiation by the same anion. The basic initiator is a catalyst. We propose to call it (including or not the chain initiation) the NCA anion mechanism in harmony with the other mechanisms.



3.5 Cross Over Reactions

Since three mechanisms of chain initiation and three mechanisms of chain growth with their proper active species coexist in the reaction mixture, cross over reactions between wrong species can take place. The most important reactions will be the attacks of the highly electrophilic N-acylated NCA chain end by the wrong nucleophiles. However, all these undesired reactions seem to be less significant than they could be feared, since none of them proceeds by the shift of equilibrium of the type of reaction (xix). Some other factors also tend to limit their extent : in most polymerizations proceeding principally through the NCA anion mechanism, the concentrations of HA, amino end group and $^{\ominus}A$ anion are generally small. In particular, the initiator anion, which is by far more reactive than the two others, is nearly inexistent when equilibrium (xxvii$_b$) sets up in the later phase of the polymerization. On the other hand, reaction (xxxiv), if it takes place, certainly consumes the active sites of polymerization but, fortunately, does not terminate the chain growth, since the active groups situated on the other ends of the reacting chains, at least that of P chain in this reaction, are preserved. The reaction is the condensation of two chains and corresponds to a very fast chain growth.



The other combination, i.e. reaction of NCA anion with the electrophile of the wrong mechanism, NCA monomer, is well known. It is simply the reaction of chain initiation (self-initiation) by the NCA anion mechanism, reaction (xxv).

4. SIGNIFICANCE OF EACH ELEMENTARY MECHANISM

In the preceding section we drew up the list of all the normal reactions likely present in the general polymerization mixtures, without taking account of their significance. In reality, the significance of these reactions varies widely, from predominant to inexistent in certain cases, according to the nature of the reagents and the polymerization conditions. In the following part of the discussion the situation will be examined for various combinations of monomers and initiators and the significance of these reactions will be qualitatively evaluated.

4.1 Standard Polymerizations

4.1.1 Primary amine initiation

In general, primary amines are only moderately basic and give equilibrium (xxii$_a$) rather shifted to the left. Therefore, the chain initiation is principally due to the action of the base itself (B = HA'), reaction (xxiii), with a slight participation of NCA anion, reaction (xxv). Under these conditions, the major part of the basic initiators is rapidly incorporated into one of the ends of the resulting chain, while carbamic acid appears on the other. However, the latter cannot remain as such and decarboxylates for the most part in the absence of a highly basic acceptor of proton. The resulting amino end group, although less basic than the original initiator, ensures a certain basicity to the reaction mixture and forms carbamate salt with the remainder of chains non decarboxylated. Thus, free amino end group is present in majority over carbamate group in the later phase of the polymerization. However, since the polymerization by carbamate anion, reaction (xxix), is much faster than the aminolytic polymerization, reaction (xxviii), from the kinetical point of view, the part of the reaction by carbamate anion often presents a higher significance than that of the aminolytic reaction (Ref. 33, 34). The participation of the NCA anion mechanism, reaction (xxx), is small for the primary amine initiated polymerization, in which the basicity of the reaction mixture decreases rapidly, but it sensibly increases with the bulkiness of the initiator for the secondary amine initiated reaction (Ref. 25 - 27).

4.1.2 Tertiary amine initiation

Tertiary amines are in general fairly basic, apart from some exceptions (aromatic amines, weakly basic). In the pre-initiation equilibrium, reaction (xxii$_a$), the only active species of the polymerization is NCA anion, and the chain initiation takes place wholly through the corresponding mechanism, reaction (xxv). The concentration of the initiator does not decrease. The resulting carbamate group remains in this form when its concentration is under the limit tolerated by the basicity of the reaction mixture, and decarboxylates beyond it. This limit is still fairly low because of the certain acidity, hence a low stabilizing ability, of the tertiary ammonium cation given by the catalyst amine. Thus, in the later phase of the polymerization, most chains possess N-acylated NCA unit on the one end and free amino group on the other, while the remainder carries the former and carbamate group. Kinetically, the polymerization involves above all the NCA anion mechanism, reaction (xxx), which is probably contaminated by a non-negligible part of carbamate anion mechanism, reaction (xxix), and a very small part of aminolytic mechanism, reaction (xxviii).

4.1.3 Basic salt initiation

4.1.3.1 Strongly basic salts from extremely weak acids. This is the case of triphenylmethylsodium (Ref. 16), fluorenylpotassium (Ref. 61, 62) and sodium hydride (Ref. 65). Acid-basic equilibrium (xxii$_b$), is completely shifted to the right and the chain initiation takes place only by the attack of NCA anion, reaction (xxv). The resulting polymer chain possesses one carbamate anion which does not decarboxylate and one N-acylated NCA end unit. Therefore, the polymerization involves both the carbamate anion mechanism, reaction (xxix), and the NCA anion mechanism, reaction (xxx). We have some indices which allow to believe that, from the kinetical point of view, the latter is fairly more significant than the former (see paragraph 4.2.2). There is no place for the aminolytic mechanism, reaction (xxviii).

4.1.3.2 Strongly basic salts from very weak acids. Alkaline alcoholates (Ref. 16) and lactam salts (Ref. 17), for example belong to this category. Their conjugate acids, HA, are nearly as acidic as or still less acidic than the current NCAs such as those of glycine, alanine and γ-benzyl-L-glutamate. Besides, since, NCA is used in a higher concentration than the initiator, equilibrium (xxii$_b$) is rather shifted to the right, but the initiator anion is now present in a certain ratio in the reaction mixture. Both the initiator anion and NCA anion participate in the chain initiation, respectively through reactions (xxiv) and (xxv). More chains are formed than those in the foregoing paragraph. A small portion of initiation takes place by the action of HA, through reaction (xxiii). The resulting chain possesses for the most part carbamate end group and N-acylated NCA end unit. Practically no place is reserved for the aminolytic mechanism, reaction (xxviii), unless a portion of very weak acid (e.g. methanol) is added to increase the number of chains (see paragraph

4.2.2). Chain growth proceeds by the carbamate anion mechanism, reaction (xxix), and the NCA anion mechanism, reaction (xxx), the latter being more significant from the kinetical point of view. Cross over reactions (xxxi) and (xxxiii), in particular the latter, are feared especially when the polymerization is slow.

4.1.3.3 Weakly basic salts. The title covers sodium acetate (Ref. 126), sodium benzoate and sodium 3-hydantoin-acetate (Ref. 118). Equilibrium (xxii$_b$) is shifted rather to the left. The initiator anion being lowly efficient, only a small number of chains are initiated by reaction (xxiv) and carry a linear anhydride end group. This group is sooner or later converted into N-acylated NCA unit by the attack of NCA anion. The principal part of the initiation is due to the small concentration of NCA anion that is formed. Carbamate group of the resulting chain easily decomposes into free amino group in the presence of the conjugate acid of the initiator, and the chain growth is ensured only by the NCA anion mechanism and the aminolytic mechanism. After all, the composition of the polymerization mixture resembles that using tertiary amine initiators, except the high concentration of the initiator, necessary because of its low basicity.

4.2 Particular NCAs

4.2.1 N-substituted NCAs

The chain initiation of the polymerization of N-substituted NCAs ($R^3 \neq H$) by the action of basic salt initiators can take place through various reactions. When the initiator anion is nucleophilic enough (e.g. methoxide anion), it acts directly as an initiating species, reaction (xxiv). When it is strongly basic but not highly nucleophilic (e.g. triphenylmethyl anion), it deprotonates NCA on 4-position and the resulting NCA carbanion initiates the polymerization in the same manner as does methoxide anion. In both cases, the chain growth proceeds by the carbamate anion mechanism, reaction (xxix). For tertiary amine initiators, the situation is similar. When the initiator amine is basic enough (e.g triethylamine), it deprotonates NCA on 4-position. The addition of protic impurities, more acidic than the monomer, facilitates the initiation. When a weakly basic amine (e.g. pyridine) is used in high concentration, a part of it attacks directly 5-CO of NCA, which leads to the formation of a betain type zwitter-ion in this case. The chain growth involves in any case both the carbamate anion mechanism, reaction (xxix), and the aminolytic mechanism, reaction (xxviii), with a relative significance which varies with the basicity of the reaction mixture.

4.2.2 α-Aminoisobutyric acid NCA

The title compound (dimethylglycine NCA) is a 4,4-disubstituted oxazoline-2,5-dione. Because of the double substitution on α-carbon of amino acid, its mixed anhydride group is only weakly electrophilic (or its carbonyl groups lowly polarized) and it is one of the least acidic (Ref. 101) and the least reactive (Ref. 126, 127) NCAs. In the study of the mechanism of NCA polymerization, these low electrophilicity and low reactivity are useful, because they accentuate certain phenomena which cannot be observed when highly reactive NCAs are used. Thus, while only the very highly electrophilic N-acetylglycine NCA "co-initiates" the polymerization of current NCAs by serving as a chain initiator (Ref. 128), its model compounds, less electrophilic, also give a similar effect and accelerate the polymerization of α-aminoisobutyric acid NCA in the tertiary amine catalyzed polymerization (Ref. 101).

When sodium methoxide is used as the initiator, equilibrium of this NCA with sodium methoxide, reaction (xxii$_b$) sets up in a middle position, giving rise to significant chain initiations both by the initiator anion, reaction (xxiv), and NCA anion, reaction (xxv). It is noticeably displaced to the left when a portion of methanol, the conjugate acid of the initiator, is added. The polymerization is then accelerated as a whole, by the great increase of the concentration of the initiator anion, hence that of the significance of reaction (xxiv), without much affecting in proportion that of NCA anion. This leads us to believe that NCA anion exists still in majority over the initiator anion in the original equilibrium before the addition of methanol, and that the former is less efficient than the latter in the reactions of initiation. In contrast, the rate of polymerization by the carbamate anion mechanism, reaction (xxix), deduced from the increment of conversion due to the addition of methanol, corresponds only to a small fraction of that of the polymerization by NCA anion, reaction (xxx), and this means that the former is much slower than the latter.

CONCLUSION

The hypothesis of coexistence of three mechanisms controlled by the acid-basic equilibria between different active species was presented. It was shown to account for most experimental results of the base initiated polymerizations of NCAs, although it leaves to prove still many points in the future.

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