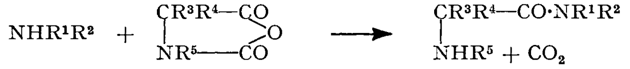
77. *Reactions of* N-*Carboxy-α-amino-acid Anhydrides catalysed by Tertiary Bases.*

By D. G. H. Ballard and C. H. Bamford.

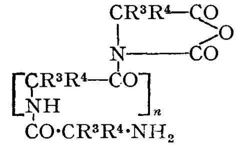
The kinetics of polymerisation of *N*-carboxy-DL-phenylalanine anhydride catalysed by tri-*n*-butylamine are consistent with a reaction mechanism similar to that already proposed for initiation by salts of weak carboxylic acids : bifunctional intermediates with terminal anhydride and basic groups are formed, and enter into coupling reactions. The main difference between the two systems appears to be catalysis of the coupling reaction by tertiary base.

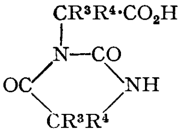
Possible reactions which limit the degree of polymerisation are discussed.

In previous papers [1] we described investigations of the mechanism of polymerisation of *N*-carboxy-α-amino-acid anhydrides (I) when primary or secondary bases or salts are used as initiators. The reactions appear to differ significantly with the two classes of initiator, as regards both mechanism and products. The main process occurring with primary or secondary bases is the normal propagation reaction involving terminal base groups :

(I)  . . . . (1)

and the products are linear polypeptides. Initiation by salts, which is confined to those *N*-carboxy-anhydrides having unsubstituted NH groups, leads to bifunctional intermediates of the type (II) :

(II) 

 (III)

which, by virtue of their free basic groups, participate in reactions with *N*-carboxy-anhydride molecules similar to (1), or enter into a different type of polymerisation process involving the terminal anhydride resides.[1d] Kinetic analysis has shown that coupling of the bifunctional intermediates is one of the most important reactions in the polymerisation. Cyclisation of (II; $n = 0$) in which the amino-group reacts with the amide carbonyl group yields derivatives of 3-hydantoinylacetic acid (III), which under certain conditions may be a major product.[1c] An alternative cyclisation ($n > 1$) involving the other carbonyl group produces cyclic polypeptides, of which some of the lower members (*e.g.*, cyclic hexaglycine) have been obtained crystalline. It is possible that other chain-breaking reactions occur which lead to linear, and not cyclic, polypeptides.[1d]

In this paper we discuss the reactions initiated by tertiary bases. The polymerisation of *N*-carboxy-anhydrides in the presence of tertiary bases, especially pyridine, is a well-known method of preparing polypeptides. There is great confusion in the literature about the reactivity of *N*-carboxy-anhydrides to tertiary bases. Wessely,[2] who first observed the pyridine-catalysed reaction, reported that other tertiary bases (*e.g.*, trimethylamine) are inactive. Ballard, Bamford, and Weymouth [1c] showed, however, that anhydrides which are not *N*-substituted react readily with other tertiary amines in polar media, yielding cyclic peptides (excluding dioxopiperazines) and derivatives of 3-hydantoinylacetic acid. There has also been controversy as to whether traces of water are necessary for these reactions.[3] For *N*-substituted carboxy-anhydrides Ballard, Bamford, and Weymouth [1c] showed that no reaction occurs between the sublimed anhydrides and purified

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[1] (*a*) Ballard and Bamford, *Proc. Roy. Soc.*, 1954, *A*, **223**, 495; Ballard, Bamford, and Weymouth, (*b*) *Nature*, 1954, **174**, 173; (*c*) *Proc. Roy. Soc.*, 1954, *A*, **227**, 155; (*d*) Ballard and Bamford, *Chem. Soc. Sp. Publ. No*, 2, 1955, p. 25.

[2] Wessely, *Z. physiol. Chem.*, 1925, **146**, 72.

[3] Cf., *e.g.*, Hanby, Waley, and Watson, *J.*, 1950, 3009; Coleman, *J.*, 1950, 3222.

tertiary bases, even in polar media. These results conflict with those of Bilek, Derkosch, Michl, and Wessely,[4] but we believe that their systems contained initiating impurites; although the pyridine used was carefully dried, the anhydrides were not sublimed and the manipulation was not carried out under conditions which precluded the presence of water; for a fuller discussion of this matter see Ballard and Bamford.[1d] As a result of many experiments in which the reagents have been purified with the utmost care we conclude that only those anhydrides with an unsubstituted NH group react at an appreciable rate with tertiary bases. The rate of reaction in these cases is sensitive to the nature of the medium, being higher in polar liquids. There seem to be no grounds for believing that traces of water are necessary for reaction, nor is there any essential difference between pyridine and other tertiary bases. The *N*-substituted anhydrides, if they react at all, do so only extremely slowly by comparison.

A kinetic investigation of the reaction between *N*-carboxy-DL-phenylalanine anhydride and tri-*n*-butylamine in nitrobenzene is described below.

EXPERIMENTAL

Purification of Materials.—*N*-Carboxy-DL-phenylalanine anhydride, prepared by the general methods described by Hanby, Waley, and Watson,[3] was purified by recrystallisation from ethyl acetate–benzene until free from chloride. Immediately before use it was sublimed at $<10^{-3}$ mm.

Tri-*n*-butylamine, from the Eastman-Kodak Corp., was fractionated, kept over barium oxide for at least 48 hr., and distilled in a vacuum.

Nitrobenzene was treated with phosphoric oxide overnight, decanted, treated with barium oxide, and distilled. It was then kept overnight over barium oxide and again distilled.

Methods.—The sealed vessels containing the purified reagents were introduced into a dry box, in which all the subsequent manipulations necessary for preparing the reaction mixture were carried out. The rate of reaction was measured manometrically in a constant-volume apparatus, similar to that described by Waley and Watson.[5] Concentrations of tertiary base in nitrobenzene were determined (on samples removed from the dry-box) by potentiometric titration with an antimony electrode after addition of ethanol containing about 5% of water.[1a]

Some determinations of the intrinsic viscosities of the polymers were carried out. Mixtures of the anhydride and tertiary base in nitrobenzene were allowed to react overnight; the polymers were then precipitated by addition of ether, washed with ether, and dried in a vacuum. Their intrinsic viscosities were measured in dichloroacetic acid.

RESULTS AND DISCUSSION

Kinetics.—Fig. 1 shows typical conversion–time curves which indicate that at the lower base concentrations the reaction ceases before the anhydride has reacted completely. This is to be attributed to the formation of the substituted 3-hydantoinylacetic acid, which is a strong acid and neutralises the initiating base. At higher base concentrations the conversion is complete. Titration shows that the yield of acid is quite small, corresponding to about 2% of the anhydride. However, in order to avoid complications due to acid formation we have measured only intial rates of reaction.

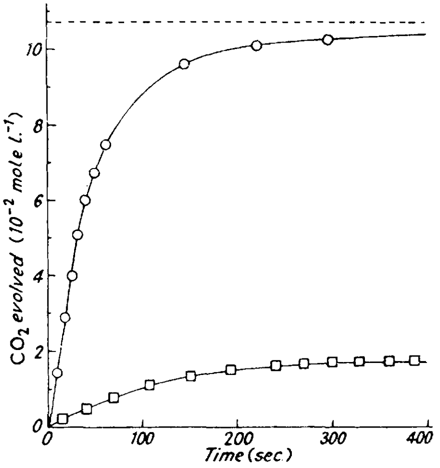
Fig. 2 shows the dependence of the initial rate of reaction on the initial concentration of anhydride $[M]_0$, for different concentrations of (total) base $[T]_0$, at 25°. The order with respect to $[M]_0$ is evidently somewhat greater than one. Similar results were obtained at 15°. The dependence of rate on base concentration at constant $[M]_0$ is shown in Fig. 3 for 25° and 15°. In both cases the overall order in base concentration is slightly less than one. It will be clear from Fig. 3 that the reaction has a small positive temperature coefficient.

The intrinsic viscosities of the resulting poly-DL-phenylalanine measured in dichloroacetic acid are plotted in Fig. 4 against the ratio $[M]_0/[T]_0$. The results show that comparatively high degrees of polymerisation are reached (see p. 386). Further, the overall reactions leading to these high polymers are quite rapid. For example, with $[M]_0 = 1{\cdot}04$ mole l.$^{-1}$ and $[M]_0/[T]_0 = 45$, the reaction is practically complete in $\frac{1}{2}$ hr. and

[4] Bilek, Derkosch, Michl, and Wessely, *Monatsh.*, 1953, **84**, 717.
[5] Waley and Watson, *Proc. Roy. Soc.*, 1949, *A*, **199**, 499.

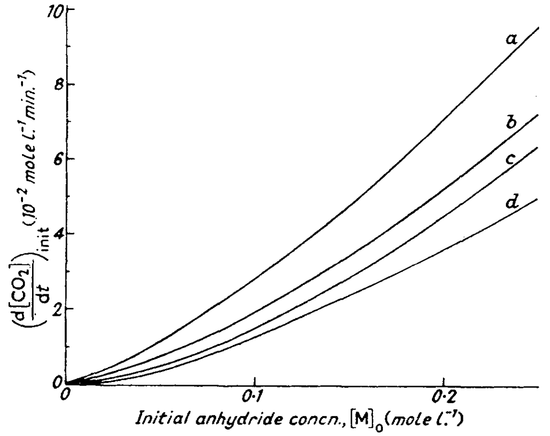
the intrinsic viscosity of the final polymer is 16, corresponding to a degree of polymerisation close to 320. The velocity coefficient [1a] of the normal propagation reaction (1) is $1{\cdot}56 \times 10^{-2}$ mole^{-1} l. sec.$^{-1}$ at 25°, so that in ½ hr. the maximum degree of polymerisation obtainable by this reaction is $1{\cdot}56 \times 10^{-2} \times 1{\cdot}04 \times 1800 = 29$ ($[M]_0$ being assumed to be constant). Clearly the situation is similar to that described for initiation by salts of weak acids, the combination of high rate and high degree of polymerisation being

FIG. 1. *Conversion–time curves for reaction of* N-*carboxy*-DL-*phenylalanine anhydride with tri*-n-*butylamine in nitrobenzene at* 25°; $[M]_0 = 0{\cdot}107$ *mole/l.*$^{-1}$.



○ $[T]_0$ (initial total base concn.) = 0·103 mole l.$^{-1}$;
□ $[T]_0 = 1{\cdot}6 \times 10^{-3}$ mole l.$^{-1}$.
Broken line corresponds to 1 mol. of CO$_2$.

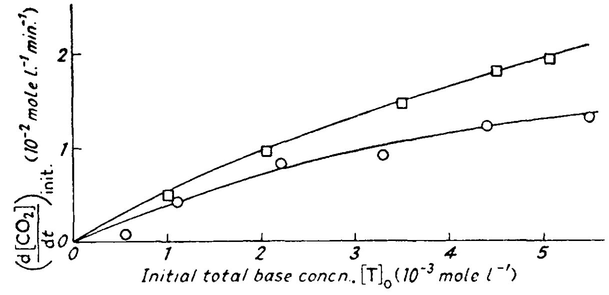
FIG. 2. *Dependence of initial rate of reaction on* N-*carboxy*-DL-*phenylalanine anhydride concentration* [M], *for different initial base concentrations*, $[T]_0$, *in nitrobenzene at* 25°.



(*a*) $[T]_0$ 8·1, (*b*) 5·0, (*c*) 4·0, (*d*) $3{\cdot}2 \times 10^{-3}$ mole l.$^{-1}$.

FIG. 3. *Dependence of initial rate of reaction on tri*-n-*butylamine concentration for* $[M]_0 = 0{\cdot}104$ *mole l.*$^{-1}$, *in nitrobenzene.*

□ At 25°.
○ At 15°.



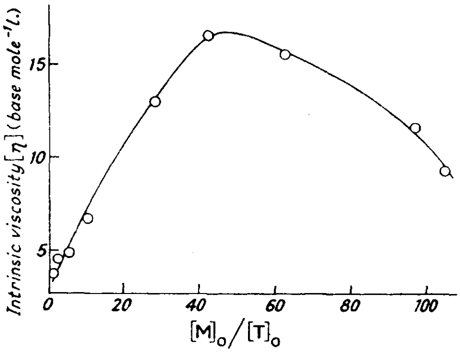


FIG. 4. *Intrinsic viscosities of polymers prepared in nitrobenzene at* 25° *as a function of* $[M]_0/[T]_0$.

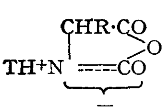
$[M]_0 = 1{\cdot}04$ mole l.$^{-1}$ in all cases.

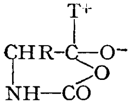
inexplicable in terms of the normal propagation reaction above. Any proposed mechanism must account not only for this fact and the kinetic behaviour of the reaction, but also for the facts that (*a*) *N*-substituted anhydrides do not react, (*b*) dioxopiperazines are not formed, and (*c*) substituted 3-hydantoinylacetic acid derivatives are formed.

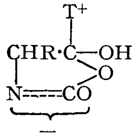
The following mechanism, which is similar to that proposed for initiation by salts of weak acids, is consistent with all the observations :

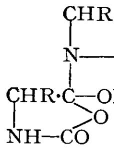
$$\left.\begin{array}{rll}
M + T & \rightleftharpoons C \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; . & K\ (a) \\
C + M & \rightleftharpoons D + T \quad . \; . \; . \; . \; . \; . \; . \; . & k_1,\ k_2\ (b) \\
D & \longrightarrow M\cdot[AR]_1\cdot X + CO_2 \; . \; . \; . \; . \; . \; . & k_3\ (c) \\
C + M\cdot[AR]_n\cdot X & \longrightarrow M\cdot[AR]_{n+1}\cdot X + CO_2 + T \; . \; . \; . \; . & k_4\ (d) \\
M\cdot[AR]_m\cdot X + M\cdot[AR]_n\cdot X & \xrightarrow{T} M\cdot[AR]_{m+n+1}\cdot X + CO_2 . \; . \; . \; . \; . & k_5\ (e) \\
M\cdot[AR]_1\cdot X & \longrightarrow \text{Substituted 3-hydantoinylacetic acid} & .\ (f) \\
M\cdot[AR]_n\cdot X & \longrightarrow \text{Cyclic polypeptide} + CO_2 \; . \; . \; . \; . \; . & .\ (g)
\end{array}\right\} (2)$$

Reaction (2*a*) represents the formation of a complex C between anhydride (M) and tertiary base molecules (T). This complex may possibly be an ion pair (IV; R = $PhCH_2$) but we think that it is more likely to be (V) or (VI) resulting from addition to the acid carbonyl group. It does not seem possible to obtain a satisfactory mechanism on the assumption that the ring is opened in the formation of the complex. The complex is considered to be in equilibrium with the reactants. Reaction between the complex and anhydride produces the dimer (VII) denoted in equation (2*b*) by D. The latter then eliminates carbon dioxide to give the bifunctional intermediate (II; $n = 0$), which is written in (2*c*) as $M\cdot[AR]_1\cdot X$. In this symbols M, X represent the anhydride and base termination respectively, and $[AR]_1$ indicates that the molecule contains one amino-acid residue in addition to M. Equation (2*d*) includes a reaction between the complex and the anhydride residue of $M\cdot[AR]_n\cdot X$. This residue is probably more reactive than the isolated anhydride molecule, so that this reaction is necessary in view of (2*b*). Reaction (2*d*) may also include a reaction between C and the X group of $M\cdot[AR]_n\cdot X$. Coupling between bifunctional intermediates is shown in (2*e*) and is considered to be catalysed by tertiary base. With the exception of this catalysis, reactions (2*c*, *d*, *e*) are identical with those postulated in the case of salt initiation. This is also true of reactions (2*f*, *g*). Since only low yields of hydantoin derivatives are formed, and comparatively high degrees of polymerisation may be attained reactions (2*f*, *g*) will be omitted from the kinetic scheme. The normal propagation reaction has also been omitted for reasons described above.


(IV)


(V)


(VI)


(VII)

Under our conditions $[M]_0 \gg [T]_0$, hence the concentration of complex is given by

$$[C] = K[M]_0[T] = \frac{K[M]_0[T]_0}{1 + K[M]_0} \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (3)$$

[T] being the concentration of free tertiary base. Applying stationary state considerations to [D] and $\sum_n(M\cdot[AR]_n\cdot X)$ ($\equiv$ [X]) we have in the early stages of the reaction :

$$d[D]/dt = k_1[C][M]_0 - k_2[D][T] - k_3[D] = 0 \quad . \; . \; . \; . \; . \; . \quad (4)$$

$$d[X]/dt = k_3[D] - k_5[T][X]^2 = 0 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \; . \quad (5)$$

Also

$$d[CO_2]/dt = k_3[D] + k_4[C][X] + k_5[T][X]^2$$

which, by (3), (4), (5) becomes

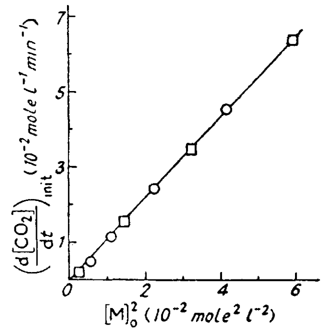
$$\frac{\mathrm{d}[\mathrm{CO_2}]}{\mathrm{d}t} = 2Kk_1[\mathrm{M}]_0{}^2\frac{[\mathrm{T}]}{\alpha[\mathrm{T}]+1} + K^{\frac{3}{2}}\left(\frac{k_1}{k_5}\right)^{\frac{1}{2}}k_4[\mathrm{M}]_0{}^2\frac{[\mathrm{T}]}{(\alpha[\mathrm{T}]+1)^{\frac{1}{2}}} \quad . \; . \; . \; . \; . \; . \; . \; . \quad (6)$$

$$= 2Kk_1[\mathrm{M}]_0{}^2\frac{[\mathrm{T}]_0}{\alpha[\mathrm{T}]_0+K[\mathrm{M}]_0+1} + K^{\frac{3}{2}}\left(\frac{k_1}{k_5}\right)^{\frac{1}{2}}k_4[\mathrm{M}]_0{}^2\frac{[\mathrm{T}]_0}{(\alpha[\mathrm{T}]_0+K[\mathrm{M}]_0+1)^{\frac{1}{2}}} \quad . \quad (7)$$

where $\alpha = k_2/k_3$.

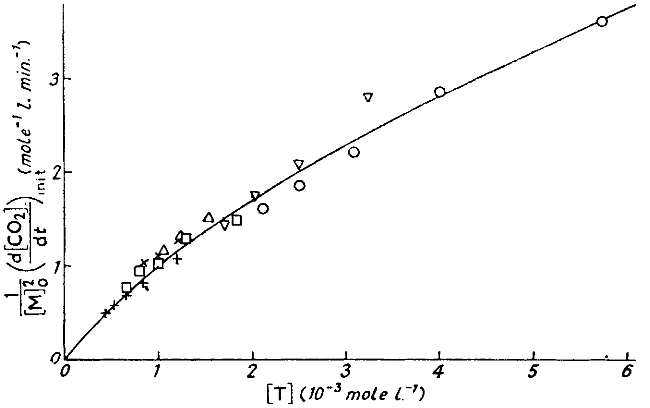
According to equation (7), at constant $[\mathrm{T}]_0$ the order in $[\mathrm{M}]_0$ lies between one and two, while at constant $[\mathrm{M}]_0$ the order in $[\mathrm{T}]_0$ is below one. Thus this mechanism leads to a rate equation with a form which might be compatible with the experimental results. The complex form of (7) makes detailed comparison with experiment difficult, but we have examined the validity of the proposed mechanism in the following way. If equation (6) is applicable, then at constant [T] the rate should show simple second-order dependence on $[\mathrm{M}]_0$. Now [T] can be calculated from $[\mathrm{T}]_0$ and $[\mathrm{M}]_0$ by equation (3) if K is known. If a value for K is assumed, corresponding values of $[\mathrm{M}]_0$ and $[\mathrm{T}]_0$ compatible with [T] = constant can be obtained from equation (3) and the rates of reaction can then be read off from Figs. 2 and 3. It appears that if K = 15 mole^{-1} l. a very satisfactory linear relation between rate and $[\mathrm{M}]_0{}^2$ is obtained under conditions calculated to give [T] = constant at 25°. This is shown in Fig. 5 for [T] = 10^{-3} mole l.$^{-1}$. This method of choosing a value of K is reasonably sensitive; thus if K is taken as high as 25 mole^{-1} l. the rate–$[\mathrm{M}]_0{}^2$ plot is concave upwards, while with K = 10 mole^{-1} l. it is concave downwards. Use of other values for [T] leads to the same value of K. A similar procedure applied to the results for 15° gives K = 25 mol.$^{-1}$ (Fig. 5). It is obviously satisfactory that K should have a negative temperature coefficient, since the forward reaction in the equilibrium (2*a*) would be expected to be exothermic. The rate–$[\mathrm{M}]_0{}^2$ plots for the two temperatures are practically coincident, the negative temperature coefficient of K balancing the positive coefficients due to the rate constants.

FIG. 5. *Initial rate of reaction in nitrobenzene as a function of* $[\mathrm{M}]_0{}^2$ *for* [T] = 10^{-3} *mole l.*$^{-1}$.



○ At 25°, K = 15 mole^{-1} l.
□ At 15°, K = 25 mole^{-1} l.

FIG. 6. *Dependence of* $(\mathrm{d}[\mathrm{CO_2}]/\mathrm{d}t)_{\text{initial}}/[\mathrm{M}]_0{}^2$ *on* [T]; *nitrobenzene solution at* 25°.



Values of T_0 (10^{-3} mole l.$^{-1}$):
○ 10, ▽ 8·1, △ 5·0, × 4·0, □ 3·2, + 2·1.

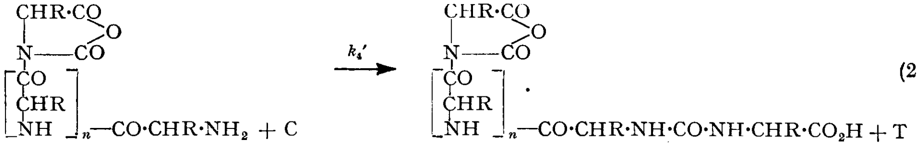
Knowing K, we can examine equation (6) further. According to this equation the rates of reaction divided by $[\mathrm{M}]_0{}^2$ when plotted against [T] should lead to a single curve, for all values of $[\mathrm{M}]_0$ and $[\mathrm{T}]_0$, at any one temperature. This is in fact the case both for 25° and 15° (see Fig. 6). It turns out that by a suitable choice of the parameters α, k_1, $k_4k_5{}^{-\frac{1}{2}}$, either of the two terms on the right of equation (6) can be made to fit the curve in Fig. 6 satisfactorily. This is not surprising since the terms are not very different in form, but it prevents an unambiguous decision as to their relative magnitudes. Some information about the values of the parameters may, however, be obtained. It follows from equation (6) that if the first term only is used for fitting the curve of Fig. 6 a minimum value of α is obtained, while use of the second term alone gives a maximum. It may be shown that the values of k_1 and $k_4(k_1/k_5)^{\frac{1}{2}}$ obtained by the use of equation (7) with the extremes of α are maximum values. The limiting values of the parameters obtained in this way are given in the Table. Numerical calculations show that any combination of the two terms on the right of equation (7) will fit the experimental results satisfactorily provided the values of the parameters used lie within the range specified in the Table The proposed mechanism is therefore satisfactory kinetically.

Temp.	K (mole^{-1} l.)	α (mole^{-1} l.) max.	α (mole^{-1} l.) min.	k_1 (mole^{-1} l. sec.$^{-1}$) max.	$k_4(k_1/k_5)^{\frac{1}{2}}$ (mol.$^{-\frac{1}{2}}$ l.$^{\frac{1}{2}}$ sec.$^{-1}$) max.
25°	15	478	148	0·64	0·35
15	25	189	83	0·38	0·15

The upper limits of k_1 given in the Table are quite close to the values of the corresponding constant deduced for initiation by sodium β-phenylpropionate.[1d] This may imply that the complexes in the two cases have reactivities of the same order, although it must be remembered that the figures tabulated represent maximum values. It is not possible from the results in the Table to estimate the magnitude of $k_4k_5^{-\frac{1}{2}}$.

Molecular Weights.—We now discuss the results shown in Fig. 4. Determinations of the intrinsic viscosities of low polymers (degree of polymerisation <50) prepared by direct initiation of the polymerisation of *N*-carboxy-DL-phenylalanine anhydride by DL-phenylalanine dimethylamide have shown that in this range the degree of polymerisation is proportional to the intrinsic viscosity. If this linear relation holds for higher polymers of the type we are considering, an intrinsic viscosity of 10 will correspond to a 200-mer. Differences in molecular-weight distribution may vitiate this relationship, which should therefore only be regarded as giving an approximate idea of the size of the polymers.

It will be seen that a maximum in Fig. 4 corresponds to $[M]_0/[T]_0$ = *ca.* 45. The fall-off in molecular weight at the lower base concentrations is probably due to the formation of the substituted 3-hydantoinylacetic acid. This, being a strong acid, neutralises the tertiary base and also the primary base groups of the bifunctional intermediates $M{\cdot}[AR]_n{\cdot}X$. Thus at low base concentrations the conversion is found to be less than 100%, and the coupling reaction (2*e*) is retarded. At high base concentrations the molecular weight increases as the base concentration decreases. So far we have not considered any reactions which control the size of the final polymers in this range of base concentrations. Clearly a reaction must occur which effectively destroys one or both of the end groups of the intermediates $M{\cdot}[AR]_n{\cdot}X$ otherwise unlimited coupling could occur. One such reaction could be (2*d'*) similar to (2*d*), but with the X group of $M{\cdot}[AR]_n{\cdot}X$ adding to the amide carbonyl group of the complex C :

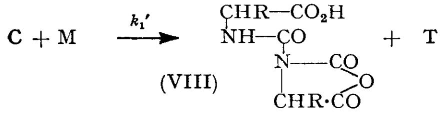


(2*d'*)

The product of reaction (2*d'*) is monofunctional, and hence can act as a chain-breaker. The instantaneous mean degree of polymerisation $\bar{P}_{\text{inst.}}$ is readily calculated for the experimentally important case in which the chains are long. It is given by :

$$\bar{P}_{\text{inst.}} = \frac{2k_4}{k_4'} + \frac{4(k_1k_5)^{\frac{1}{2}}(1 + K[M])^{\frac{1}{2}}}{K^{\frac{1}{2}}k_4'(\alpha[T]_0 + K[M] + 1)^{\frac{1}{2}}} \quad . \; . \; . \; . \; . \; . \; . \; . \quad (8)$$

Further reactions which could limit the degree of polymerisation are "wrong way" additions of C to M, or C to C, producing monofunctional molecules (VIII) in both cases, *e.g.* :



(VIII)

. . . . (9)

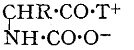
The anhydride residue of the compound (VIII) can react with the basic end of $M\cdot[AR]_n\cdot X$ and hence form a monofunctional molecule. If reaction (9) proceeds at a rate $k_1'[C][M] = Kk_1'[M]^2[T]$, the instantaneous degree of polymerisation for long chains [governed solely by reaction (9)] is given by :

$$\bar{P}_{\text{inst.}} = \frac{4k_1(1 + K[M])}{k_1'(\alpha[T]_0 + K[M] + 1)} + \frac{2K^{\frac{1}{2}}(k_1/k_5)^{\frac{1}{2}}k_4(1 + K[M])^{\frac{1}{2}}}{k_1'(\alpha[T]_0 + K[M] + 1)^{\frac{1}{2}}} \quad . \quad . \quad . \quad . \quad (10)$$

If reaction (9) involves two C molecules (velocity coefficient k_1'') instead of C and M, $\bar{P}_{\text{inst.}}$ will be given by an equation derived from (10) by replacing k_1' by $k_1''K[T]_0/(1 + K[M])$.

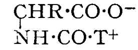
All three mechanisms predict that $\bar{P}_{\text{inst.}}$ should increase as $[T]_0$ decreases at constant [M], and are therefore in qualitative agreement with experiment. We may note that the C–C reaction leads to the strongest dependence of $\bar{P}_{\text{inst.}}$ on $[T]_0$, and reaction (2*d'*) to the weakest. In view of the obvious uncertainties we do not consider it worth while pursuing the quantitative implications of these termination mechanisms at present.

Other Reaction Mechanisms.—Wieland [6] suggested a mechanism for the interaction of tertiary bases and *N*-carboxy-anhydrides according to which the anhydride reacts in the ionic forms :



$$\begin{array}{l}\text{CHR}\cdot\text{CO}\cdot\text{T}^+\\ \text{NH}\cdot\text{CO}\cdot\text{O}^-\end{array}$$

and



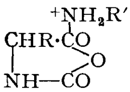
$$\begin{array}{l}\text{CHR}\cdot\text{CO}\cdot\text{O}^-\\ \text{NH}\cdot\text{CO}\cdot\text{T}^+\end{array}$$

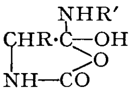
Any mechanism of this type in which the primary reaction of the tertiary base produces ring opening appears unsatisfactory for several reasons. First, it cannot differentiate between *N*-substituted anhydrides and those containing a free NH group. Secondly, it would be expected that large yields of the corresponding dioxopiperazines would be obtained, whereas these substances are not formed at all in the absence of water or other active impurities. Further, the reactions which have to be postulated to account for the nature of the products seem unlikely. Rather similar arguments against the occurrence of Wieland-type reactions in salt-catalysed polymerisations have been given by Ballard and Bamford.[1d]

The difference in behaviour between anhydrides which are *N*-substituted and those which are not seems to indicate that the reaction must proceed through the dimer (VII). If this is admitted it is difficult to produce a mechanism significantly different from that in scheme (2). The apparently high rate of chain growth in these systems is, on this view, mainly accounted for by the coupling reaction (2*e*). This type of mechanism is also satisfactory in that it accounts for the formation of 3-hydantoinylacetic acid derivatives by steps which are chemically reasonable.

The mechanism of polymerisation initiated by tertiary bases is therefore different from that of the reactions brought about by primary or secondary bases. This is understandable if the complex C has the structure (VI). Such a complex is unlikely to be formed with primary or secondary bases; in these cases normal addition to the acid carbonyl group would proceed through the structure (IX), ultimately leading to (X). The protons of the endocyclic NH groups are not involved in this process, and reactions of the type (2*b*) will not occur. In an earlier paper [1a] we have suggested that removal of a proton from the

(IX)





(X)

hydroxyl group of a complex such as (X) facilitates ring opening, since it allows the resonance energy of the peptide group being formed to assist the process. An effect of this kind would be expected to be much less important in the case of (VI) on account of the comparatively low resonance energy of the group $^+T\cdot CO\cdot$. The failure of tertiary bases to produce ring opening in the initial step is therefore not surprising.

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[6] Wieland, *Angew. Chem.*, 1951, **63**, 7; 1954, **66**, 507.