to the expression of the catalytic properties of metals.

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EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF BIOPHYSICS, WEIZMANN INSTITUTE OF SCIENCE]

Theoretical Analysis of the Polymerization Kinetics of N-Carboxy-α-amino Acid Anhydrides

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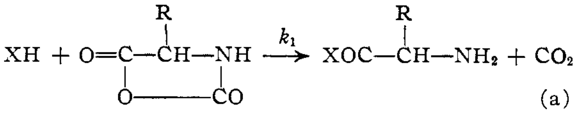
A theoretical analysis is given for the kinetics of polymerization of N-carboxy-α-amino acid anhydrides, assuming an initiation reaction (a), with a specific rate constant k_1, a propagation reaction (b), with a specific rate constant k_2, and termination reactions (c) and (d), with the respective specific rate constants k_3 and k_4. Formulas were derived for the rate of polymerization and for the rate of carbon dioxide evolution as well as for the molecular weight distribution and average degrees of polymerization of the still growing chains, characterized by free terminal amino groups, and of the terminated peptide chains, characterized by terminal carboxyl groups. From the general treatment three special cases were derived. Case I, $k_1 = k_2$; $k_3 = k_4 = 0$. The formulas given for this case were shown to agree with those derived by Flory[3] for the polymerization of ethylene oxide as well as with those of Ballard and Bamford[5] deduced for the polymerization of N-carboxy-DL-phenylalanine anhydride and N-carboxy-DL-leucine anhydride initiated by preformed polymer. Case II, $k_1 \neq k_2$; $k_3 = k_4 = 0$. The formulas for this case were found identical with those of Breitenbach and Allinger[6] derived for the polymerization of N-carboxy-DL-phenylalanine anhydride initiated by amines of different basicity. Case III, $k_1 = k_2$; $k_3 = k_4$. The variation with time of the molecular weight distribution of the growing and terminated chains was calculated assuming particular values for k_2 and k_3. It was shown that while the molecular weights of the terminated chains are spread over a wide range, the molecular weights of the unterminated chains are concentrated in the high molecular weight fraction of the polymer. Possible methods for the evaluation of k_1, k_2, k_3 and k_4 are suggested and the conditions necessary for the preparation of poly-α-amino acids of high molecular weight are discussed.

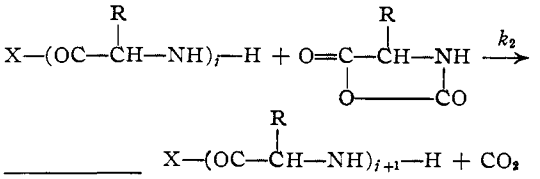
In a previous article[1] it has been shown by Sela and Berger that the polymerization of N-carboxy-α-amino acid anhydrides initiated by amines or alcohols (XH, X = R_1R_2N or RO) involves not only initiation and propagation reactions (a) and (b), but also a termination reaction (c) (see below). In the initiation reaction the X-residue of the initiator attaches itself to the C-5 carbonyl of the oxazolidine-2,5-dione, carbon dioxide is evolved, and a free amino group appears. During propagation new peptide bonds are formed as a result of the reaction of the free amino groups of the growing chains with the C-5 carbonyl groups of the anhydride. There is, however, no change in the total number of the amino groups. The termination reaction (c) causes the disappearance of the free amino groups of the growing chains as a result of their interaction with the C-2 carbonyl groups and the formation of peptides with terminal carboxyl groups adjacent to an urea link.[2] It is obvious that the catalyst may be eliminated from the system by analogous termination reaction (d).

Initiation:



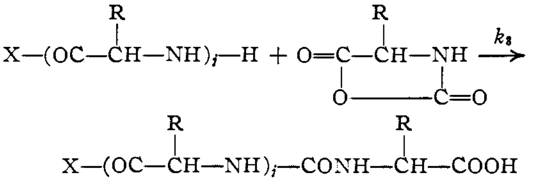
$$\mathrm{XH} + \underset{\mathrm{O}\text{———}\mathrm{CO}}{\mathrm{O{=}C{-}\overset{R}{C}H{-}NH}} \xrightarrow{k_1} \mathrm{XOC{-}\overset{R}{C}H{-}NH_2 + CO_2} \qquad \text{(a)}$$

Propagation:

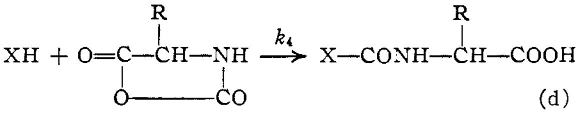


$$\mathrm{X{-}(OC{-}\overset{R}{C}H{-}NH)_{\mathit{j}}{-}H} + \underset{\mathrm{O}\text{———}\mathrm{CO}}{\mathrm{O{=}C{-}\overset{R}{C}H{-}NH}} \xrightarrow{k_2} \mathrm{X{-}(OC{-}\overset{R}{C}H{-}NH)_{\mathit{j}+1}{-}H + CO_2} \qquad \text{(b)}$$

Termination:



$$\mathrm{X{-}(OC{-}\overset{R}{C}H{-}NH)_{\mathit{j}}{-}H} + \underset{\mathrm{O}\text{———}\mathrm{C{=}O}}{\mathrm{O{=}C{-}\overset{R}{C}H{-}NH}} \xrightarrow{k_3} \mathrm{X{-}(OC{-}\overset{R}{C}H{-}NH)_{\mathit{j}}{-}CONH{-}\overset{R}{C}H{-}COOH} \qquad \text{(c)}$$



$$\mathrm{XH} + \underset{\mathrm{O}\text{———}\mathrm{CO}}{\mathrm{O{=}C{-}\overset{R}{C}H{-}NH}} \xrightarrow{k_4} \mathrm{X{-}CONH{-}\overset{R}{C}H{-}COOH} \qquad \text{(d)}$$

In the following a general kinetic analysis of a polymerization, proceeding according to the scheme described above, will be given. From the general treatment some limiting cases of special interest will be derived.

General Case.—Here it will be assumed that the polymerization is determined by four different constants k_1, k_2, k_3 and k_4, of the reactions (a), (b), (c) and (d), respectively. The concentration of the N-carboxy-α-amino acid anhydride is denoted by (M), the concentration of the catalyst by (XH), the concentration of the "growing monomer," consisting of one amino acid residue and containing a free terminal amino group by N_1^*, and the concentration of a growing peptide composed of j amino acid residues and containing a free terminal amino group by N_j^*. The rate of disappearance of catalyst is given by eq. 1, the rate of formation of a growing monomer by eq. 2, and the rate of formation of a growing j-mer by eq. 3.

$$-\frac{\mathrm{d(XH)}}{\mathrm{d}t} = (k_1 + k_4)(\mathrm{M})(\mathrm{XH}) \qquad (1)$$

$$\frac{\mathrm{d}N_1^*}{\mathrm{d}t} = k_1(\mathrm{M})(\mathrm{XH}) - (k_2 + k_3)(\mathrm{M})N_1^* \qquad (2)$$

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[1] M. Sela and A. Berger, THIS JOURNAL, **77**, 1893 (1955). *Cf.* also M. Sela and A. Berger, *ibid.*, **75**, 6350 (1953).

$$\frac{\mathrm{d}N_j^*}{\mathrm{d}t} = k_2(\mathrm{M})N^*_{j-1} - (k_2 + k_3)(\mathrm{M})N_j^* \qquad (3)$$

$$j = 2, 3, 4 \ldots\ldots \infty$$

Introducing a new variable

$$\nu = \int_0^t (\mathrm{M})\mathrm{d}t;\ \textit{i.e.},\ \mathrm{d}\nu = (\mathrm{M})\mathrm{d}t$$

the above equations become, respectively

$$-\frac{\mathrm{d(XH)}}{\mathrm{d}\nu} = (k_1 + k_4)(\mathrm{XH}) \qquad (4)$$

$$\frac{\mathrm{d}N_1^*}{\mathrm{d}\nu} = k_1(\mathrm{XH}) - (k_2 + k_3)N_1^* \qquad (5)$$

$$\frac{\mathrm{d}N_j^*}{\mathrm{d}\nu} = k_2N^*_{j-1} - (k_2 + k_3)N_j^* \qquad (6)$$

$$j = 2, 3, 4 \ldots\ldots \infty$$

Integration of (4) then gives

$$(\mathrm{XH}) = (\mathrm{XH})_0e^{-(k_1+k_4)\nu} \qquad (7)$$

where $(\mathrm{XH})_0$ is the initial concentration of catalyst. Substituting (XH) from (7) into (5) and solving for N_1^*, one obtains

$$N_1^* = \frac{k_1(\mathrm{XH})_0}{(k_1 + k_4) - (k_2 + k_3)}\left[e^{-(k_2+k_3)\nu} - e^{-(k_1+k_4)\nu}\right]$$

Letting $a = (k_1 + k_4) - (k_2 + k_3)$, the above equation becomes

$$N_1^* = \frac{k_1}{a}(\mathrm{XH})_0e^{-(k_2+k_3)\nu}\,(1 - e^{-a\nu}) \qquad (8)$$

Solving equations 6, the following expression is obtained for N_j^*

$$N_j^* = \frac{k_1}{k_2}(\mathrm{XH})_0e^{-(k_2+k_3)\nu}\left(-\frac{k_2}{a}\right)^j\left[e^{-a\nu} - \sum_{m=0}^{j-1}\frac{(-a\nu)^m}{m!}\right]$$

or

$$N_j^* = \frac{k_1}{k_2}(\mathrm{XH})_0e^{-(k_2+k_3)\nu}\left(\frac{k_2}{a}\right)^j\sum_{m=j}^{\infty}(-1)^{j+m}\frac{(a\nu)^m}{m!} \qquad (9)$$

The concentration of the free terminal amino groups of the polymer at any instant t is given by $\sum_{j=1}^{\infty} N_j^*$, and can be evaluated from (9)

$$\sum_{j=1}^{\infty} N_j^* = \frac{k_1}{a + k_2}(\mathrm{XH})_0e^{-k_3\nu}\,(1 - e^{-(a+k_2)\nu}) \qquad (10)$$

Equation 10 shows that at large values of ν the decrease in the number of free amino groups will be determined mainly by the termination constant k_3.

The number of amino acid residues in the growing polymer is given by

$$\sum_{j=1}^{\infty} jN_j^* = \frac{k_1}{(a + k_2)^2}(\mathrm{XH})_0e^{-k_3\nu}[(a + k_2)k_2\nu + a(1 - e^{-(a+k_2)\nu})] \qquad (11)$$

and the number average degree of polymerization, $\overline{P_\mathrm{n}^*}$ by

$$\overline{P_\mathrm{n}^*} = \frac{\sum_{j=1}^{\infty} jN_j^*}{\sum_{j=1}^{\infty} N_j^*} = \frac{1}{(a + k_2)}\left[a + \frac{(a + k_2)k_2\nu}{1 - e^{-(a+k_2)\nu}}\right] \qquad (12)$$

At large values of ν, when $e^{-(a+k_2)\nu} \ll 1$ and $a \ll (a + k_2)k_2\nu$, $\overline{P_\mathrm{n}^*} = k_2\nu$. At these ν values the number average degree of polymerization of the growing chains is directly proportional to ν.

The value of $\sum_{j=1}^{\infty} j^nN_j^*$ for any integral number n is (*cf.* Appendix eq. 5*)

$$\sum_{j=1}^{\infty} j^nN_j^* = \frac{k_1}{k_2}(\mathrm{XH})_0e^{-(k_2+k_3)\nu}\left(q\frac{\partial}{\partial q}\right)^n\left[\frac{q}{1 - q}(e^{-a\nu} - e^{-a\nu q})\right] \qquad (13)$$

where $q = -k_2/a$ and the differential operator $\left(q\frac{\partial}{\partial q}\right)$ designates differentiation of the term in square brackets with respect to q, and subsequent multiplication by q; the exponent $(\ )^n$ designates that this process is to be applied n times.

For the particular case $n = 2$

$$\sum_{j=1}^{\infty} j^2N_j^* = \frac{k_1}{(a + k_2)^2}(\mathrm{XH})_0e^{-k_3\nu}\left\{k_2\nu\,[(1 + k_2\nu)(a + k_2) + 2a] + \frac{a(a - k_2)}{a + k_2}\cdot(1 - e^{-(a+k_2)\nu})\right\} \qquad (14)$$

The weight average degree of polymerization, $\overline{P_\mathrm{w}^*}$, can be derived from (14) and (11)

$$\overline{P_\mathrm{w}^*} = \frac{\sum_{j=1}^{\infty} j^2N_j^*}{\sum_{j=1}^{\infty} jN_j^*} = \frac{k_2\nu[(1 + k_2\nu)(a + k_2) + 2a] + \frac{a(a - k_2)}{(a + k_2)}\times(1 - e^{-(a+k_2)\nu})}{(a + k_2)k_2\nu + a(1 - e^{-(a+k_2)\nu})} \qquad (15)$$

When $e^{-(a+k_2)\nu} \ll 1$ and $(a + k_2)k_2\nu \gg a$, (15) becomes

$$\overline{P_\mathrm{w}^*} \approx k_2\nu + \frac{a(a - k_2)}{(a + k_2)^2\,k_2\nu}$$

In most cases the second term will be negligible in comparison with $k_2\nu$, so that $\overline{P_\mathrm{w}^*}$ will approach $\overline{P_\mathrm{n}^*}$ at large values of $k_2\nu$. This indicates that the molecular weight distribution curve of the peptide fraction containing free amino groups is rather sharp even in the general case under consideration.

N-Carboxy-α-amino acid anhydride is consumed in each of the reactions in the polymerization scheme, (a), (b), (c) and (d). The over-all rate of polymerization is thus given by

$$-\frac{\mathrm{d(M)}}{\mathrm{d}t} = (k_1 + k_4)(\mathrm{XH})(\mathrm{M}) + (k_2 + k_3)\sum_{j=1}^{\infty} N_j^*(\mathrm{M}) \qquad (16)$$

i.e.

$$-\frac{\mathrm{d(M)}}{\mathrm{d}\nu} = (k_1 + k_4)(\mathrm{XH}) + (k_2 + k_3)\sum_{j=1}^{\infty} N_j^* \qquad (17)$$

Substituting the values of (XH) and $\sum_{j=1}^{\infty} N_j^*$ given by equations 7 and 10, and integrating with respect to ν from $\nu = 0$ to $\nu = \nu$, one obtains

$$\frac{(\mathrm{M})_0 - (\mathrm{M})}{(\mathrm{XH})_0} = (1 - e^{-(k_1+k_4)\nu})\left[1 - \frac{(k_2 + k_3)k_1}{(a + k_2)(k_1 + k_4)}\right] + (1 - e^{-k_3\nu})\frac{(k_2 + k_3)k_1}{k_3(a + k_2)} \qquad (18)$$

Since carbon dioxide is evolved only in the initiation and propagation reactions, the rate of gas evolution is given by

$$\frac{\mathrm{d(CO_2)}}{\mathrm{d}t} = k_1(\mathrm{XH})(\mathrm{M}) + k_2 \sum_{j=1}^{\infty} N_j^*(\mathrm{M}) \qquad (19)$$

i.e.

$$\frac{\mathrm{d(CO_2)}}{\mathrm{d}\nu} = k_1(\mathrm{XH}) + k_2 \sum_{j=1}^{\infty} N_j^* \qquad (20)$$

Substituting the values of (XH) and $\sum_{j=1}^{\infty} N_j^*$ given by equations 7 and 10, and integrating from 0 to ν, one obtains

$$\frac{(\mathrm{CO_2})}{(\mathrm{XH})_0} = \frac{k_1}{a + k_2}\left[a\,\frac{1 - e^{-(k_1 + k_4)\nu}}{k_1 + k_4} + \frac{k_2}{k_3}(1 - e^{-k_3\nu})\right] \qquad (21)$$

The rate of formation of terminated peptide chains is determined by the equations

$$\frac{\mathrm{d}N_1}{\mathrm{d}\nu} = k_4(\mathrm{XH}) \qquad (22)$$

$$\frac{\mathrm{d}N_j}{\mathrm{d}\nu} = k_3 N^*_{j-1} \qquad j = 2, 3, 4, \ldots\ldots \infty \qquad (23)$$

In these equations N_j denotes the concentration of the peptides composed of j-amino acid residues and containing a terminal carboxyl group.

Substituting the value of (XH) from (7) into (22) and solving for N_1, one obtains

$$N_1 = \frac{k_4}{k_1 + k_4}(\mathrm{XH})_0(1 - e^{-(k_1 + k_4)\nu}) \qquad (24)$$

The general expression for N_j is obtained by solving equation 23.

$$N_j = \frac{k_3 k_1}{k_2}\left(\frac{k_2}{a}\right)^{j-1}(\mathrm{XH})_0 \sum_{m=j-1}^{\infty} (-1)^{m+j-1}\frac{a^m}{m!} \int_0^{\nu} \nu^m e^{-(k_2 + k_3)\nu}\,\mathrm{d}\nu \qquad (25)$$

$$j = 2, 3, 4 \ldots\ldots \infty$$

Each of the integrals appearing in the summation represents an incomplete Gamma function.[2] The value of N_j can then be calculated numerically if desired.

The concentration of the free carboxyl groups in the reaction mixture at any instant t is given by $\sum_{j=1}^{\infty} N_j$, the value of which may be obtained from (24) and (10*) (*cf.* Appendix)

$$\sum_{=1}^{\infty} N_j = N_1 + \sum_{j=2}^{\infty} N_j = (\mathrm{XH})_0\left[1 - \frac{k_1}{a + k_2}e^{-k_3\nu} - e^{-(k_1 + k_4)\nu}\left(1 - \frac{k_1}{a + k_2}\right)\right] \qquad (26)$$

This expression may also be obtained from the following consideration: the total concentration of growing chains and terminated chains at any given time equals $(\mathrm{XH})_0 - (\mathrm{XH})$, thus

$$(\mathrm{XH})_0 - (\mathrm{XH}) = \sum_{j=1}^{\infty} N_j^* + \sum_{j=1}^{\infty} N_j$$

Inserting the value of (XH) from (7), and the value of $\sum_{j=1}^{\infty} N_j^*$ from (10) and solving for $\sum_{j=1}^{\infty} N_j$ equation 26 is obtained.

The value of $\sum_{j=2}^{\infty} j^n N_j$ for any integral number n is derived in the Appendix (*cf.* eq. 9*).

$$\sum_{j=2}^{\infty} j^n N_j = \frac{k_3 k_1}{k_2}(\mathrm{XH})_0\left(\frac{\partial}{\partial q}q\right)^n\left[\frac{q}{1 - q}\left(\frac{1 - e^{-(k_1 + k_4)\nu}}{k_1 + k_4} - \frac{1 - e^{-(k_2 + k_3 + aq)\nu}}{k_2 + k_3 + aq}\right)\right] \qquad (27)$$

where $q = -k_2/a$ and the operator $\left(\frac{\partial}{\partial q}q\right)$ designates multiplication of the term in square brackets by q and subsequent differentiations with respect to q; the exponent $(\ )^n$ designates that this process is to be applied n times.

When $n = 1$ (27) gives

$$\sum_{j=2}^{\infty} jN_j = \frac{k_3 k_1}{(a + k_2)^2}(\mathrm{XH})_0\left[(2a + k_2)\left(\frac{e^{-(k_1 + k_4)\nu} - 1}{k_1 + k_4} - \frac{e^{-k_3\nu} - 1}{k_3}\right) - \frac{k_2(a + k_2)}{k^2_3}(k_3\nu e^{-k_3\nu} + e^{-k_3\nu} - 1)\right] \qquad (28)$$

The number average degree of polymerization $\overline{P_\mathrm{n}} = \sum_{j=1}^{\infty} jN_j \Big/ \sum_{j=1}^{\infty} N_j$, of the terminated chains can be calculated from (24), (28) and (26); the weight average degree of polymerization $\overline{P_\mathrm{w}} = \sum_{j=1}^{\infty} j^2 N_j \Big/ \sum_{j=1}^{\infty} jN_j$ from (27) ($n = 2$), (24) and (28).

The formulas derived enable the calculation of the number and weight average degrees of polymerization of the polymer in the reaction mixture, composed of growing as well as of terminated chains.

Special Cases. (I) $k_1 = k_2$; $k_3 = k_4 = 0$.—In this case no termination occurs and the specific rate of initiation equals the specific rate of propagation. The well-known polymerization of ethylene oxide initiated by glycol[3] falls into this category. It has also been shown that the polymerization of N-carboxy-α-amino acid anhydrides is governed by the formulas to be deduced for this case, provided that esters or amides of amino acids or peptides composed of the same amino acid residues as the anhydride, are used as initiators, and that the termination reaction is negligible.[4,5]

When $k_1 = k_2$; $k_3 = k_4 = 0$, (7) becomes

$$(\mathrm{XH}) = (\mathrm{XH})_0 e^{-k_2\nu} \qquad (7a)$$

and (8) becomes

$$N_1^* = k_2(\mathrm{XH})_0 e^{-k_2\nu} \lim_{a \to 0} \frac{1 - e^{-a\nu}}{a} = (\mathrm{XH})_0 k_2 \nu e^{-k_2\nu} \qquad (8a)$$

The concentration, N_j^*, of the growing chains is obtained from (9)

$$N_j^* = (\mathrm{XH})_0 e^{-k_2\nu} \lim_{a \to 0}\left[\left(\frac{k_2}{a}\right)^j \sum_{m=j}^{\infty} (-1)^{j+m}\frac{(a\nu)^m}{m!}\right] = (\mathrm{XH})_0 \frac{(k_2\nu)^j}{j!} e^{-k_2\nu} \qquad (9a)$$

This equation gives a Poisson chain length distri-

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[2] K. Pearson, "Tables of the Incomplete Gamma Functions," Cambridge University Press, New York, N. Y., 1951.

[3] P. J. Flory, THIS JOURNAL, **62**, 1561 (1940).

[4] S. G. Waley and J. Watson, *Proc. Roy. Soc.* (*London*), **199A**, 499 (1949).

[5] D. G. H. Ballard and C. H. Bamford, *ibid.*, **233A**, 495 (1954).

bution of the same form as that obtained by Flory[3] and Waley and Watson.[4]

The value of $\sum_{j=1}^{\infty} N_j^*$ for the present case can be derived from (10); an identical expression being obtained by inserting the value of (XH) from equation 7a into $\sum_{j=1}^{\infty} N_j^* = (\mathrm{XH})_0 - (\mathrm{XH})$

$$\sum_{j=1}^{\infty} N_j^* = (\mathrm{XH})_0(1 - e^{-k_2\nu}) \qquad (10\mathrm{a})$$

For the case under consideration eq. 11 gives

$$\sum_{j=1}^{\infty} jN_j^* = (\mathrm{XH})_0 k_2\nu \qquad (11\mathrm{a})$$

The number average degree of polymerization, $\overline{P_n}^*$, can be obtained from (12), or by dividing (11a) by (10a)

$$\overline{P_n^*} = \frac{k_2\nu}{1 - e^{-k_2\nu}} \qquad (12\mathrm{a})$$

When $e^{-k_2\nu} \ll 1$, $\overline{P_n^*} = k_2\nu$.

The value of $\sum_{j=1}^{\infty} j^2N_j$ is obtained from (14)

$$\sum_{j=1}^{\infty} j^2N_j^* = (\mathrm{XH})_0 k_2\nu(1 + k_2\nu) \qquad (14\mathrm{a})$$

The weight average degree of polymerization may be obtained from (15) or by dividing (14a) by (11a)

$$\overline{P_w^*} = 1 + k_2\nu \qquad (15\mathrm{a})$$

Equations 12a and 15a show that when $k_2\nu \gg 1$, $P_n^* = P_w^*$, as is to be expected for a Poisson distribution.

The rate of carbon dioxide evolution in this case equals the rate of disappearance of the anhydride and follows from (19)

$$\frac{\mathrm{d(CO_2)}}{\mathrm{d}t} = -\frac{\mathrm{d(M)}}{\mathrm{d}t} = k_2(\mathrm{XH})_0(\mathrm{M}) \qquad (19\mathrm{a})$$

remembering that $(\mathrm{XH})_0 = (\mathrm{XH}) + \sum_{j=1}^{\infty} N_i^*$ and $k_1 = k_2$.

From eq. 19a it is obvious that the polymerization discussed is a first-order reaction with respect to the anhydride M.

The amount of gas evolved as a function of ν is obtained from (21)

$$\frac{(\mathrm{CO_2})}{(\mathrm{XH})_0} = \frac{(\mathrm{M})_0 - (\mathrm{M})}{(\mathrm{XH})^0} = k_2\nu \qquad (21\mathrm{a})$$

At the end of the polymerization ($t = \infty$), when (M) = 0, (21a) becomes $k_2\nu = (\mathrm{M})_0/(\mathrm{XH})_0$. This is in accord with our previous conclusion that $\overline{P_n^*} = k_2\nu = (\mathrm{M})_0/(\mathrm{XH})_0$ when $k_2\nu \gg 1$. As no termination takes place, the number average degree of polymerization of the final polymer is inversely proportional to the initial concentration of catalyst and directly proportional to the initial concentration of anhydride.

The recent elaborate kinetic analysis by Ballard and Bamford[5] of the polymerization kinetics of N-carboxy-α-amino acid anhydrides initiated by preformed polymers, can be reduced formally to the case under consideration. The propagation reaction proceeds, according to the above authors, through an intermediate complex Y_{m+1}, formed by the interaction of a growing chain X_m, composed of m-amino acid residues, with an anhydride molecule. Y_{m+1} decomposes with carbon dioxide evolution to give the propagated chain X_{m+1}. Free amines and the acids RNHCOOH and $\mathrm{RNH_3^+}$ present in the reaction mixture as a result of the interaction of carbon dioxide with the free terminal amino groups of the growing chains act as catalysts in the above decomposition reaction. Assuming a stationary state (*i.e.*, $\mathrm{d}Y/\mathrm{d}t = 0$), Ballard and Bamford[5] derived a set of equation similar to (3), when $k_3 = 0$. The polymerization scheme suggested by the above authors enabled them to explain their interesting observation that the rate of polymerization of N-carboxyleucine anhydride and N-carboxyphenylalanine anhydride is independent of carbon dioxide pressure, while the rate of polymerization of N-carboxysarcosine anhydride is enhanced by increasing the carbon dioxide pressure. Since no termination reaction was assumed by Ballard and Bamford[5] the presence of terminated chains was ignored.

(II) $k_1 \neq k_2$, $k_3 = k_4 = 0$.—In this case no termination reaction occurs and the velocity constant of initiation differs from that of propagation. The kinetic treatment given by Breitenbach and Allinger[6] for the polymerization of N-carboxy-α-amino acid anhydrides initiated by a variety of catalysts corresponds to this case.

When $k_1 \neq k_2$ and $k_3 = k_4 = 0$, (7) gives

$$(\mathrm{XH}) = (\mathrm{XH})_0 e^{-k_1\nu} \qquad (7\mathrm{b})$$

equation 8 gives

$$N_1^* = \frac{k_1}{k_1 - k_2}(\mathrm{XH})_0 e^{-k_2\nu}(1 - e^{-(k_1 - k_2)\nu}) \qquad (8\mathrm{b})$$

and (9) becomes

$$N_i^* = \frac{k_1}{k_2}(\mathrm{XH})_0 e^{-k_2\nu}\left(\frac{k_2}{k_2 - k_1}\right)^i \sum_{m=j}^{\infty} \frac{(k_2 - k_1)^m\nu^m}{m!} \qquad (9\mathrm{b})$$

It can be easily verified that eq. 9b is identical with the expression derived by Ballard and Bamford[5] for the molecular weight distribution of an amino acid polymer obtained under conditions corresponding to the special case II.

The concentration of the terminal amino groups of the polymer is obtained from (10)

$$\sum_{j=1}^{\infty} N_i^* = (\mathrm{XH})_0(1 - e^{-k_1\nu}) \qquad (10)$$

The rate of carbon dioxide evolution, or the rate of disappearance of the anhydride, from the reaction mixture, will be given by

$$\frac{\mathrm{d(CO_2)}}{\mathrm{d}t} = -\frac{\mathrm{(dM)}}{\mathrm{d}t} = k_1(\mathrm{XH})(\mathrm{M}) + k_2\sum_{j=1}^{\infty} N_i^*(\mathrm{M}) \qquad (19\mathrm{b})$$

As. $(\mathrm{XH}) + \sum_{j=1}^{\infty} N_j^* = (\mathrm{XH})_0$, it follows that $k_1(\mathrm{XH}) \gg k_2 \sum_{j=1}^{\infty} N_j^*$ at the beginning of the reaction. At this stage $-\mathrm{d(M)}/\mathrm{d}t \approx k_1(\mathrm{XH})_0(\mathrm{M})$ and the polymerization reaction is of first order with respect to the anhydride. As the polymeriza-

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(6) J. W. Breitenbach and K. Allinger, *Monatsh.*, **84**, 1103 (1953).

tion proceeds, and $k_2 \sum_{j=1}^{\infty} N_j^*$ becomes considerably larger than k_1(XH), the polymerization reaction is given by $-\mathrm{d(M)}/\mathrm{d}t \approx k_2\mathrm{(XH)_0(M)}$. At this stage the reaction is again of first order with respect to the anhydride. The constant k_1 will thus determine the rate of carbon dioxide evolution at the beginning of the reaction, while the constant k_2 will determine the rate of gas evolution toward the end of the reaction.

Equations 11b and 12b, derived from (11) and (12), respectively, give $\sum_{j=1}^{\infty} jN_j^*$ and $\overline{P_n}^*$ for this case

$$\sum_{j=1}^{\infty} jN_i^* = \mathrm{(XH)_0}\left[k_2\nu + \left(1 - \frac{k_2}{k_1}\right)(1 - e^{-k_1\nu})\right] \quad \text{(11b)}$$

$$\overline{P_n}^* = \frac{k_2\nu}{1 - e^{-k_1\nu}} + \left(1 - \frac{k_2}{k_1}\right) \quad \text{(12b)}$$

Equation 12b shows that if $k_1 \gg k_2$, the number average degree of polymerization at the times when $e^{-k_1\nu} \ll 1$ will be given, just as in case I, by $\overline{P_n}^* \approx k_2\nu$. On the other hand, if $k_1 \ll k_2$ and provided that $k_1\nu \ll 1$, the number average degree of polymerization, $\overline{P_n}^*$, equals unity. Beginning with times corresponding to $k_1\nu \gg 1$, $\overline{P_n}^*$ starts to increase since for these times $e^{-k_1\nu} \ll 1$, $k_2\nu \gg k_2/k_1$, so that $\overline{P_n}^* \approx k_2\nu$.

(III) $k_1 = k_2$, $k_3 = k_4$.—In this case a termination reaction occurs and the reactivity of the initiator is equal to that of the growing chains. The formulas to be deduced will hold for the polymerization of N-carboxy-α-amino acid anhydride, initiated by an amide or ester of the corresponding amino acid or peptide, and terminated by reaction (c).

The concentration of the catalyst is derived from (7)

$$\mathrm{(XH)} = \mathrm{(XH)_0}\, e^{-(k_2 + k_3)\nu} \quad \text{(7c)}$$

and the concentration of the growing chains from (8) and (9)

$$N_1^* = k_2\mathrm{(XH)_0}e^{-(k_2 + k_3)\nu} \lim_{a \to 0} \frac{1 - e^{-a\nu}}{a} = \mathrm{(XH)_0}k_2\nu e^{-(k_2 + k_3)\nu} \quad \text{(8c)}$$

$$N_j^* = \mathrm{(XH)_0}e^{-(k_2 + k_3)\nu}(k_2)^j \lim_{a \to 0} \frac{1}{a^j} \sum_{j=1}^{\infty} (-1)^{j+m} \frac{(a\nu)^m}{m!} = \mathrm{(XH)_0} \frac{(k_2\nu)^j}{j!} e^{-(k_2 + k_3)\nu} \quad \text{(9c)}$$

$$j = 2, 3, 4 \ldots\ldots \infty$$

Equation 9c shows that the molecular weight distribution of the growing chains is determined by a Poisson function multiplied by $e^{-k_3\nu}$.

The time $\bar{\nu}$ at which the molar concentration of a growing chain of a given degree of polymerization j reaches its maximal value is obtained by determining the value of ν at which $\partial N_j^*/\partial\nu = 0$. One finds $\bar{\nu} = j/(k_2 + k_3)$.

The degree of polymerization j of the growing chain having the highest molar concentration at a given time ν is obtained by determining the value of j at which $\partial N_j^*/\partial j = 0$. It is found that $\bar{j} = k_2\nu$.

The full lines in Fig. 1 and Fig. 2 illustrate the molecular weight distribution of the growing chains on a number basis for several different times $(k_2 + k_3)\nu$. In Fig. 1 it was assumed that k_2 = 0.1 liter mole^{-1} sec.$^{-1}$ and k_3 = 0.003 liter mole^{-1} sec.$^{-1}$,

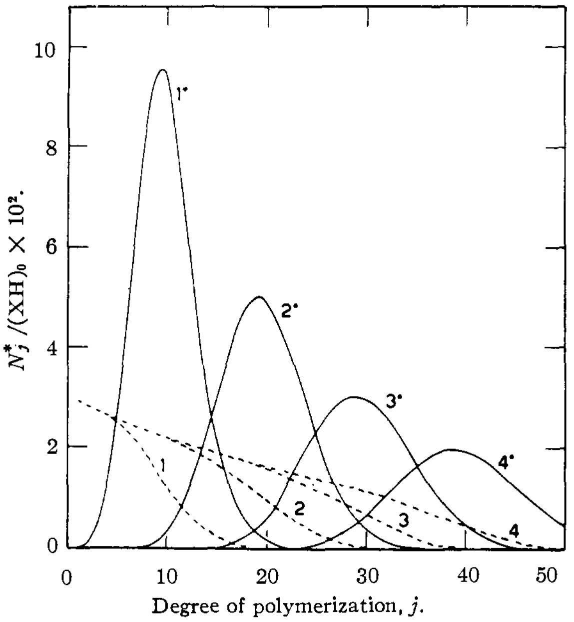

Fig. 1.—Molecular weight distribution on a number basis assuming k_2 = 0.1 liter mole^{-1} sec.$^{-1}$ and k_3 = 0.003 liter mole^{-1} sec.$^{-1}$ The curves 1*, 2*, 3* and 4* (full line) give the molecular weight distribution of the growing chains at times corresponding to $(k_2 + k_3)\nu$ = 10, 20, 30 and 40, respectively, while the curves 1, 2, 3 and 4 (dotted line) give the molecular weight distribution of the terminated chains at the same times.

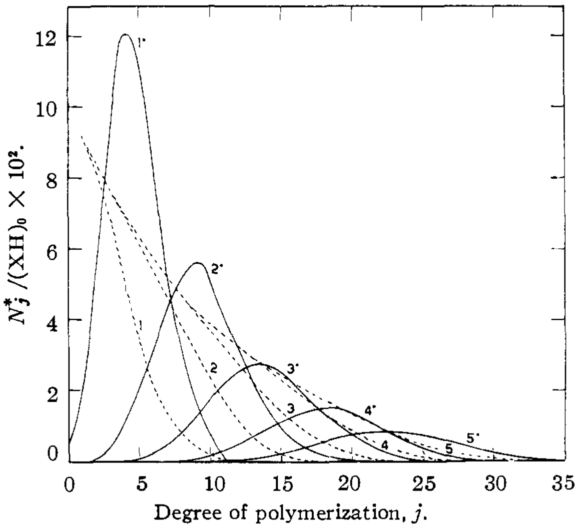

Fig. 2.—Molecular weight distribution on a number basis assuming k_2 = 0.1 liter mole^{-1} sec.$^{-1}$ and k_3 = 0.01 liter mole^{-1} sec.$^{-1}$ The curves 1*, 2*, 3*, 4* and 5* (full line) give the molecular weight distribution of the growing chains at times corresponding to $(k_2 + k_3)\nu$ = 5, 10, 15, 20 and 25, respectively, while the curves 1, 2, 3, 4 and 5 (dotted line) give the molecular weight distribution of the terminated chains at the same times.

while in Fig. 2 it was assumed that $k_2 = 0.1$ liter mole^{-1} sec.$^{-1}$ and $k_3 = 0.01$ liter mole^{-1} sec.$^{-1}$.

The total concentration of the free amino groups of the growing chains derived from (10)

$$\sum_{j=1}^{\infty} N_j^* = (\mathrm{XH})_0 e^{-k_3\nu}(1 - e^{-k_2\nu}) \qquad (10c)$$

Equation 10c shows that the total number of free amino groups in the polymer increases in the first stages of the reaction and decreases as the polymerization proceeds. The increase in concentration of the NH_2-groups is governed by the term $1 - e^{-k_2\nu}$ containing the initiation constant $k_1 = k_2$, while the decrease in the NH_2-groups is determined by the factor $e^{-k_3\nu}$, containing the termination constant k_3.

From (11) one obtains

$$\sum_{j=1}^{\infty} jN_j^* = (\mathrm{XH})_0 k_2 \nu e^{-k_3\nu} \qquad (11c)$$

A comparison of eq. 11a, given for the case where no termination occurs, with eq. 11c, shows that in the former case the weight of the polymer increases gradually with ν, whereas in the present case the weight of the fraction composed of growing chains decreases after some time as a result of the termination reaction.

Equations 11c and 10c enable the calculation of the number average degree of polymerization of the growing chains (*cf.* also eq. 12)

$$\overline{P_n^*} = \frac{k_2\nu}{1 - e^{-k_2\nu}} \qquad (12c)$$

It is of interest to note that the value of $\overline{P_n^*}$ in this case is identical with its value when no termination takes place (*cf.* eq. 12a).

The expression $\sum_{j=1}^{\infty} j^2N_j^*$ is obtained from (14)

$$\sum_{j=1}^{\infty} j^2N_j^* = (\mathrm{XH})_0 k_2\nu(1 + k_2\nu)e^{-k_3\nu} \qquad (14c)$$

The value of the weight average degree of polymerization $\overline{P_w^*} = 1 + k_2\nu$, obtained from (15) or from (14c) and (11c), is also identical with its value when no termination occurs (eq. 15a).

The rate of carbon dioxide evolution in this case is obtained by inserting the values of (XH) and $\sum_{j=1}^{\infty} N_j^*$ from equations 7c and 10c, respectively into (20)

$$\frac{\mathrm{d}(\mathrm{CO_2})}{\mathrm{d}\nu} = k_2(\mathrm{XH})_0 e^{-k_3\nu} \qquad (20c)$$

A comparison of (19a) with (20c) shows that when the polymerization is characterized only by a propagation reaction, the rate of carbon dioxide evolution with respect to ν is proportional to the initial concentration of catalyst and is independent of the time ν; in the present case, however, the rate of gas evolution remains proportional to the initial concentration of catalyst, but as a result of the termination reaction diminishes with the time ν.

On integration (20c) gives

$$(\mathrm{CO_2}) = \frac{k_2}{k_3}(\mathrm{XH})_0(1 - e^{-k_3\nu}) \qquad (21c)$$

As the rate of carbon dioxide evolution differs in the present case from the rate of anhydride disappearance, it is of interest to compare these two values. By dividing (16) by (19) one obtains

$$-\frac{\mathrm{d}(\mathrm{M})}{\mathrm{d}(\mathrm{CO_2})} = \frac{k_2 + k_3}{k_2} = 1 + \frac{k_3}{k_2} \qquad (29)$$

Equation 29 shows that in the present case the rate of anhydride consumption is proportional to the rate of carbon dioxide evolution.

Integration of (29) gives

$$\int_{\mathrm{M}}^{\mathrm{M}_0} \mathrm{d}(\mathrm{M}) = \left(1 + \frac{k_3}{k_2}\right)\int_0^{\mathrm{CO_2}} \mathrm{d}(\mathrm{CO_2})$$

i.e.

$$(\mathrm{M})_0 - (\mathrm{M}) = (\mathrm{CO_2})\left(1 + \frac{k_3}{k_2}\right) \text{ or } \frac{(\mathrm{M})_0 - (\mathrm{M})}{(\mathrm{CO_2})} = 1 + \frac{k_3}{k_2} \qquad (30)$$

When the polymerization is brought to completion, (M) = 0 and

$$(\mathrm{M})_0/(\mathrm{CO_2}) = 1 + k_3/k_2$$

The difference, $[(\mathrm{M})_0 - (\mathrm{M})] - (\mathrm{CO_2})$, of course gives the concentration of the carboxyl groups present in the reaction mixture. Thus

$$(\mathrm{COOH}) = \frac{k_3}{k_2}(\mathrm{CO_2}) \qquad (31)$$

The concentration of terminated chains composed of one amino acid residue is derived from (24)

$$N_1 = \frac{k_3}{k_2 + k_3}(\mathrm{XH})_0(1 - e^{-(k_2 + k_3)\nu}) \qquad (24c)$$

The concentration N_j of the terminated chains composed of j amino acid residues is obtained by finding $\lim_{a \to 0} N_j$ from (25)

$$N_j = (\mathrm{XH})_0 \frac{k_3k_2^{j-1}}{(j-1)!}\int_0^{\nu} \nu^{j-1} e^{-(k_2 + k_3)\nu}\,\mathrm{d}\nu \qquad (25c)$$

$$j = 2, 3, 4 \ldots\ldots \infty$$

The dotted lines in Fig. 1 and Fig. 2 illustrate the molecular weight distribution of the terminated chains on a number basis, using for k_2 and k_3 the same values as specified for the growing chains. The N_j values given were calculated numerically from (25c) after transformation into an incomplete Gamma function.[2]

Figure 3 gives the molecular weight distribution of the growing chains and terminated chains on a weight basis, for the case specified in Fig. 1. Figure 4, on the other hand, gives the corresponding molecular weight distribution for the case specified in Fig. 2.

The total number of terminated chains is obtained from (26)

$$\sum_{j=1}^{\infty} N_j = (\mathrm{XH})_0(1 - e^{-k_3\nu}) \qquad (26c)$$

when $e^{-k_3\nu} \ll 1$, $\sum_{j=1}^{\infty} N_j = (\mathrm{XH})_0$, *i.e.*, at large $k_3\nu$ values, the polymer consists of terminated chains only.

The ratio between terminal carboxyl and amino groups in the polymer is obtained from (26c) and (10c)

$$\frac{(\mathrm{COOH})}{(\mathrm{NH_2})} = \frac{\sum_{j=1}^{\infty} N_j}{\sum_{j=1}^{\infty} N_j^*} = \frac{e^{k_3\nu} - 1}{1 - e^{-k_2\nu}} \qquad (32)$$

Equation 32 shows that the ratio (COOH)/(NH_2) increases with time and approaches the value $e^{k_3\nu} - 1$ when $e^{-k_2\nu} \ll 1$.

The total number of amino acid residues in the terminated polymer is given by eq. 33 derived from (24c) and (28)

$$\sum_{=1}^{\infty} jN_j = N_j + \sum_{j=2}^{\infty} jN_j = \frac{(\mathrm{XH})_0}{k_3}\left[(k_2 + k_3)(1 - e^{-k_3\nu}) - k_2k_3e^{-k_3\nu}\right] \qquad (33)$$

The number average degree of polymerization of the terminated chains is obtained from (33) and (26c)

$$\overline{P_n} = \frac{k_2}{k_3} + 1 - \frac{k_2\nu}{e^{k_3\nu} - 1} \qquad (34)$$

If $k_2/k_3 \gg 1$, and the terminated polymer is investigated at a ν value at which $k_2/k_3 \gg k_2\nu/e^{k_3\nu} - 1$ then $\overline{P_n} = k_2/k_3$. The terminated polymer resembles in this respect many of the polymers obtained by addition polymerization.

The expression $\sum_{j=1}^{\infty} j^2N_j$ required for the evaluation of $\overline{P_w}$ is obtained from (24c) and (27) ($n = 2$)

$$\sum_{i=1}^{\infty} j^2N_j = \frac{(\mathrm{XH})_0}{k_3^2}\left[(1 - e^{-k_3\nu})(k_3^2 + 3k_2k_3 + 2k_2^2) - k_3\nu e^{-k_3\nu}(2k_2^2 + 3k_2k_3 + k_2^2k_3\nu)\right] \qquad (35)$$

Hence

$$\overline{P}_w = \frac{k_3^2 + 3k_2k_3 + 2k_2^2 - \dfrac{k_3\nu e^{-k_3\nu}(2k_2^2 + 3k_2k_3 + k_2^2k_3\nu)}{(1 - e^{-k_3\nu})}}{k_3\left[(k_2 + k_3) - \dfrac{k_2k_3\nu e^{-k_3\nu}}{(1 - e^{-k_3\nu})}\right]} \qquad (36)$$

At large enough values of ν the fractions appearing in the numerator and denominator may be neglected, and

$$\overline{P_w} = \frac{k_3^2 + 3k_2k_3 + 2k_2^2}{k_3(k_2 + k_3)} = 1 + 2(k_2/k_3) \qquad (37)$$

If $k_2/k_3 \gg 1$, $\overline{P_w} = 2(k_2/k_3)$. It follows that $\overline{P_w} = \overline{2P_n}$, a relation characteristic for polymers formed by polycondensation or by addition polymerization.

The application to the reaction mixture of the usual techniques for the isolation of the peptide fraction will obviously lead to a mixture containing unterminated as well as terminated chains. As the separation of these two types of peptide chains may be difficult, the molecular weight distribution of the total polymer is of interest, particularly wherever physicochemical studies of the unfractionated polymer are carried out. The formulas for such a distribution may be derived from the equations given above. To illustrate this ($N_j^* + N_j$) and ($jN_j^* + jN_j$) were calculated as function of j, at different times ν, for a polymerization characterized by the rate constants, k_2 and k_3, specified in Fig. 1. The results are represented in Figs. 5 and 6.

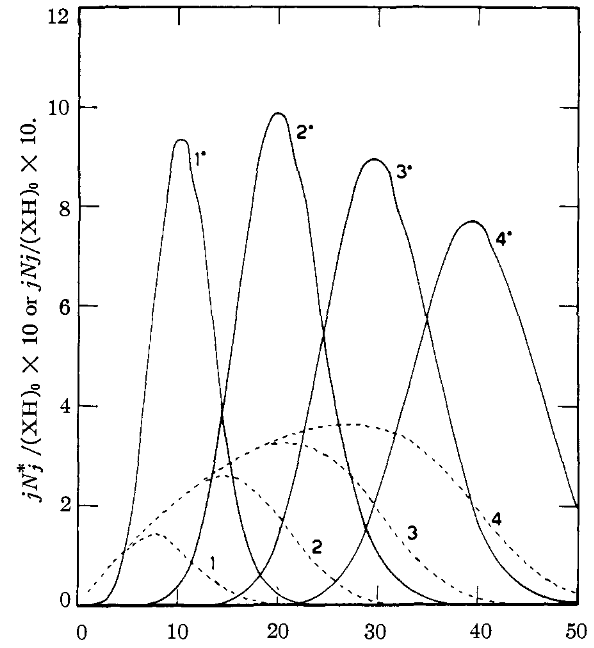

Fig. 3.—Molecular weight distribution on weight basis of the growing chains (full line) and of the terminated chains (dotted line) for the cases specified in Fig. 1.

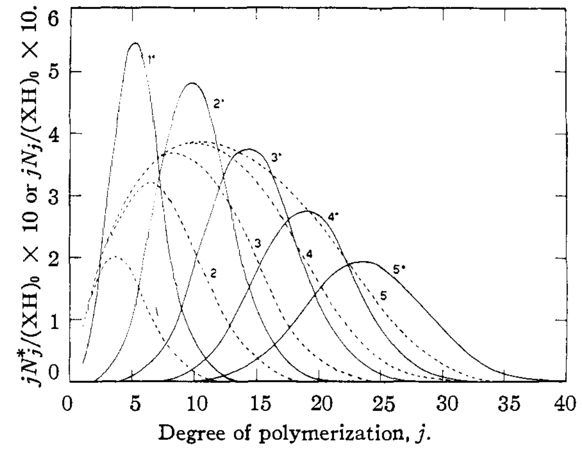

Fig. 4.—Molecular weight distribution on weight basis of the growing chains (full line) and of the terminated chains (dotted line) for the cases specified in Fig. 2.

Discussion

In the equations derived above the variable $\nu = \int_0^t (\mathrm{M})\,dt$ was introduced instead of the time variable t. The value of ν at any given time may be obtained from a graph representing (M) as a function of t. (M) can be determined experimentally using the titration method for the determination of N-carboxy-α-amino acid anhydrides,[7] or, in the special cases where no termination reaction occurs, by subtracting the total amount of the carbon dioxide

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[7] A. Berger, M. Sela and E. Katchalski, *Anal. Chem.*, **25**, 1554 (1953).

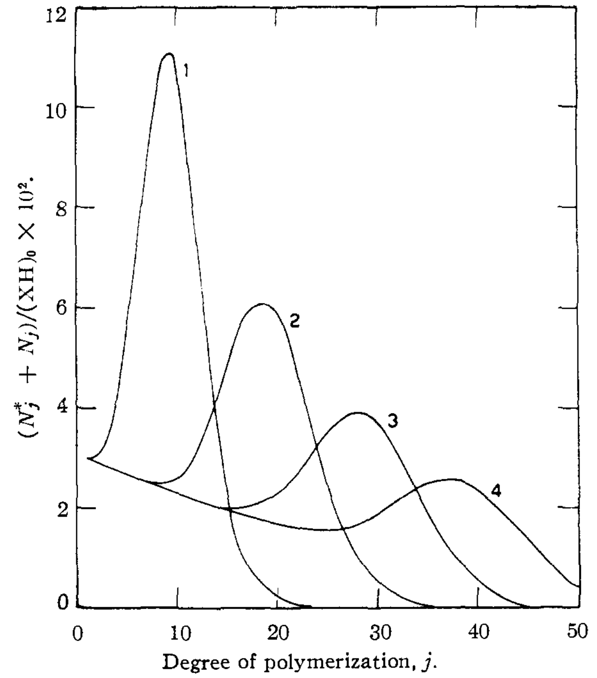

Fig. 5.—Molecular weight distribution of the total number of chains, growing and terminated, for the cases specified in Fig. 1.

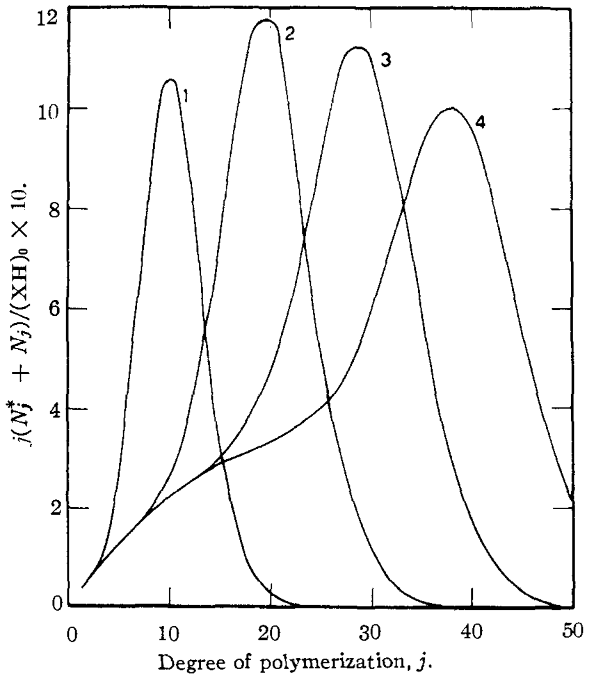

Fig. 6.—Molecular weight distribution on weight basis of the sum of growing and terminated chains for the cases specified in Fig. 1.

evolved from the initial concentration of the anhydride.

The route of polymerization of N-carboxy-α-amino acid anhydrides has been described above by means of four different constants. It seems desirable, therefore, to indicate methods which might be used for their quantitative evaluation. As this has been done in certain cases for the initiation and propagation constants some representative numerical values will be given.

When the polymerization is of first order with respect to the monomer (*cf.* case I), *i.e.*, when the termination reaction is negligible and the reactivity of the initiator is the same as that of the growing peptide chains, the propagation constant k_2 is easily calculated from the experimental data by one of the conventional kinetic techniques. Thus Ballard and Bamford[5] deduced a k_2 value of $6.0 \times 10^3 \times e^{-\frac{7630}{RT}}$ liter mole^{-1} sec.$^{-1}$ for the polymerization of N-carboxy-DL-phenylalanine anhydride in nitrobenzene which is initiated by preformed polymer. For the polymerization of the same anhydride in nitrobenzene initiated by N-ethylglycinediethylamide Breitenbach and Allinger[6] give $k_2 = 2.97 \times 10^3 \times e^{-\frac{6490}{RT}}$ liter mole^{-1} sec.$^{-1}$ The significant effect of the solvent on the propagation constant may be exemplified by the polymerization of N-carboxy-DL-leucine anhydride initiated by the corresponding preformed polymer and carried out at 45° in nitrobenzene and *o*-nitroanisole, respectively.[5] In the case of the first solvent $k_2 = 8.72 \times 10^{-2}$ liter mole^{-1} sec.$^{-1}$, and in the case of the second solvent $k_2 = 5.83 \times 10^{-2}$ liter mole^{-1} sec.$^{-1}$

The initiation constant k_1 may be calculated, even in the general case, from the rate of carbon dioxide evolution when a relatively large amount of catalyst is used (*cf.* eq. 19). Equation 19 shows that k_1 determines the rate of carbon dioxide evolution particularly at the beginning of the reaction when $(XH) \approx (XH)_0$ and $\sum_{j=1}^{\infty} N_j^* \ll (XH)$. Poor initiators such as benzyl alcohol and water will cause long induction periods,[4] while good initiators such as primary and secondary amines will start the polymerization at once. The kinetic studies of Breitenbach and Allinger[6] have shown that stronger bases are better initiators than weaker ones. For the polymerization of N-carboxy-DL-phenylalanine anhydride in nitrobenzene it was found that $k_1 = 2k_2$ at 30° when N-ethylglycinediethylamide was used as initiator, and $k_1 = k_2/6000$ at 50°, when *p*-chloroaniline was used as initiator. Ballard and Bamford[5] indicated that the dimethylamides of DL-phenylalanine and DL-leucine react with their respective anhydrides 3 to 4 times as rapidly as the corresponding higher polymers.

No data are available at present in the literature as to the magnitude of k_3. Its value may be calculated in the special case III from the concentration of the terminal carboxyl groups of the polymer fraction at any given instant (*cf.* eq. 26c). The carboxyl group content may be determined experimentally by the titration of the polymer isolated from the reaction mixture according to Sela and Berger.[1] A rough estimate of the value of k_3 can be made from the data of Breitenbach and Allinger[6] for the polymerization of N-carboxy-DL-phenylalanine anhydride in nitrobenzene at 30°. When N-ethylglycinediethylamide was used as initiator, the carbon dioxide evolved amounted to 90–98% of the initial amount of anhydride. If it is assumed that this polymerization may be described by the formulas given for case III, $(\mathrm{M})_0/(\mathrm{CO}_2) = 1 + k_3/k_2$ (*cf.* eq. 30, $(\mathrm{M}) = 0$), and since $(\mathrm{M})_0/(\mathrm{CO}_2) = 100/90$ to $100/98$ it follows that $k_3 = (1/9)k_2$ to $(1/49)k_2$. The values given by other authors[8] also seem to indicate that the magnitude of the termination constant k_3 does not exceed a few percentage of the propagation constant k_2. The relatively low value of k_3 in comparison with k_2 shows that an appreciable amount of terminated chains will appear only at relatively high degrees of polymerization.

If $k\ /k_1 \approx k_3/k_2$, k_4 will have a small effect on the rate of polymerization, as well as on the molecular weight distribution of the polyamino acid formed. Its value can, however, be determined from (17) or (24) if convenient methods for the determination of (XH) or N_1 are available.

The formulas developed for case III show that at large $k_2\nu$ values, the number average degrees of polymerization of the growing chains is proportional to $k_2\nu$, while that of the terminated chains approaches k_2/k_3. If polymers of relatively high molecular weight are required, relatively small initial concentrations of catalyst should be used, and the polymerization of anhydride carried out under conditions at which k_3 is as small as possible. The influence of solvent and temperature on k_2/k_3 is important in this respect. The retardation of the termination reaction does not only increase the average molecular weight of the polyamino acid formed, but also sharpens the distribution curve of the polymer and thus improves its homogeneity.

The molecular weight distribution curves given in Fig. 3 and Fig. 4 show that the polymer obtained as a result of a propagation as well as a termination reaction is composed of growing peptide chains which are concentrated mainly in the high molecular weight fraction, and of terminated chains which are spread over a relatively large range of molecular weights. Fractionation by precipitation, dialysis or by any other fractionating technique, of polyamino acids with molecular weight distributions similar to the ones given in Figs. 3 and 4, will enrich the content of the terminated chains in the low molecular weight fractions, and will increase the concentration of the unterminated chains in the high molecular weight fractions. The low molecular weight fractions will, therefore, be characterized by a relatively high –COOH group content and a low $\mathrm{NH_2}$– group content, while the high molecular weight fractions will be characterized by a relatively high $\mathrm{NH_2}$- content and a low -COOH content. It is thus obvious that in order to prepare polyamino acids with high average molecular weights, the high molecular weight fractions might be used effectively as initiators of polymerization of N-carboxy-α-amino acid anhydrides.

Appendix

The value of $\sum_{j=1}^{\infty} j^n N_j^*$, for any integral number n, is obtained from (9) as

$$\sum_{j=1}^{\infty} j^n N_j^* = C \sum_{j=1}^{\infty} j^n q^j \sum_{m=j}^{\infty} \frac{p^m}{m!} \qquad (1^*)$$

where $C = k_1/k_2(\mathrm{XH})_0 e^{-(k_2+k_3)\nu}$, $q = -k_2/a$ and $p = -a\nu$.

Developing the infinite series given in (1*) it can be shown that

$$C \sum_{j=1}^{\infty} j^n q^j \sum_{m=j}^{\infty} \frac{p^m}{m!} = C \sum_{m=1}^{\infty} \frac{p^m}{m!} \sum_{j=1}^{m} j^n q^j \qquad (2^*)$$

The sum $\sum_{j=1}^{m} j^n q^j$, appearing in the right hand side of (2*), may be derived from the known sum $\sum_{j=1}^{m} q^j = q(1-q^m)/(1-q)$, by the following n successive operations: $\sum_{j=1}^{m} q^j$ is differentiated with respect to q and the derivative obtained multiplied by q; the result is again differentiated with respect to q and so on. Denoting the n-fold repetition of this operation by the differential operator $\left(q\frac{\partial}{\partial q}\right)^n$, one obtains

$$\sum_{j=1}^{m} j^n q^j = \left(q\frac{\partial}{\partial q}\right)^n \left[\sum_{j=1}^{m} q^j\right] = \left(q\frac{\partial}{\partial q}\right)^n \left[\frac{q}{1-q}(1-q^m)\right] \qquad (3^*)$$

Substituting (3*) in (2*) and inserting the expression obtained into (1*), eq. 4* is finally obtained.

$$\sum_{=1}^{\infty} j^n N_j^* = C \sum_{m=1}^{\infty} \frac{p^m}{m!} \left(q\frac{\partial}{\partial q}\right)^n \left[\frac{q}{1-q}(1-q^m)\right] = C\left(q\frac{\partial}{\partial q}\right)^n \left[\frac{q}{1-q}\left(\sum_{m=1}^{\infty}\frac{p^m}{m!} - \sum_{m=1}^{\infty}\frac{(pq)^m}{m!}\right)\right] = C\left(q\frac{\partial}{\partial q}\right)^n \left[\frac{q}{1-q}(e^p - e^{pq})\right] \qquad (4^*)$$

The substitution of the values of C and p in (4*) gives

$$\sum_{j=1}^{\infty} j^n N_j^* = \frac{k_1}{k_2}(\mathrm{XH})_0 e^{-(k_2+k_3)\nu} \left(q\frac{\partial}{\partial q}\right)^n \left[\frac{q}{1-q}(e^{-a\nu} - e^{-a\nu q})\right] \qquad (5^*)$$

The value of $\sum_{j=2}^{\infty} j^n N_j$ for any integral number n is derived from (25)

$$\sum_{j=2}^{\infty} j^n N_j = \frac{k_3 k_1}{k_2}(\mathrm{XH})_0 \sum_{j=2}^{\infty} j^n \left(\frac{k_2}{a}\right)^{j-1} \sum_{m=j-1}^{\infty} (-1)^{j+m-1} \frac{a^m}{m!} \int_0^{\nu} \nu^m e^{-(k_2+k_3)\nu}\, \mathrm{d}\nu \qquad (6^*)$$

Differentiating (6*) with respect to ν and inserting C, p and q defined above (*cf.* eq. 1)

$$\frac{\partial}{\partial \nu} \sum_{j=2}^{\infty} j^n N_j = \sum_{j=2}^{\infty} j^n \frac{\mathrm{d}N_j}{\mathrm{d}\nu} = k_3 C \sum_{j=2}^{\infty} j^n q^{j-1} \sum_{m=j-1}^{\infty} \frac{p^m}{m!} \qquad (7^*)$$

By making use of the differential operator $((\partial/\partial q)q)^n$, which is analogous to the one used in eq. 3*, it can be easily verified that

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(8) E. Katchalski and M. Sela, THIS JOURNAL, **75**, 5284 (1953); A. Patchornik, M. Sela and E. Katchalski, *ibid.*, **76**, 299 (1954); K. Heyns and R. Brockmann, *Z. Naturforschung*, **9b**, 21 (1954); K. Schlögl, F. Wessely and G. Korger, *Monatsh.*, **83**, 845 (1952).

$$\frac{\partial}{\partial \nu}\sum_{j=2}^{\infty} j^n N_j = k_3 C \left(\frac{\partial}{\partial q} q\right)^n \left[\frac{q}{1-q}(e^p - e^{pq})\right] \quad (8^*)$$

Substituting the values of p and C in (8*) and integrating with respect to ν, one obtains

$$\sum_{=2}^{\infty} j^n N_j = \frac{k_3 k_1}{k_2}(\mathrm{XH})_0 \left(\frac{\partial}{\partial q} q\right)^n \left[\frac{q}{1-q}\left(\frac{1-e^{-(k_1+k_4)\nu}}{k_1+k_4} - \frac{1-e^{-(k_2+k_3+aq)\nu}}{k_2+k_3+aq}\right)\right] \quad (9^*)$$

For the special case $n = 0$, (9*) gives

$$\sum_{j=2}^{\infty} N_j = \frac{k_3 k_1}{a+k_2}(\mathrm{XH})_0 \left[\frac{e^{-(k_1+k_4)\nu} - 1}{k_1+k_4} - \frac{e^{-k_3\nu} - 1}{k_3}\right] \quad (10^*)$$

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORIES OF THE UNIVERSITY OF MELBOURNE AND THE UNIVERSITY OF BUFFALO]

The Kinetics of the Carbonate Exchange and Racemization Reactions of Carbonato-bis-(ethylenediamine)-cobalt(III) Ion[1]

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Carbon-14 was used to trace the exchange of ligand carbonate with uncomplexed carbonate ion in aqueous solution. The en salt exchanges a little more slowly than does the previously studied tetrammine analog. The isotope fractionation effect at exchange equilibrium is very small in the case of the en compound, in contrast to the tetrammine. In spite of these differences, the exchange behavior of the en complex can be reasonably explained on the basis of a mechanism not greatly modified from that proposed for the tetrammine. Optically active en complex exchanges at the same rate as does the racemate. However, the rate of racemization is very much slower than that of ligand exchange, and has very different kinetic characteristics. It is concluded that racemization is an intramolecular process, largely independent of ligand substitution reactions. Nevertheless it involves some of the same intermediates postulated in explanation of the exchange kinetics.

The exchange reaction in aqueous solution between free uncomplexed carbonate ion and the corresponding ligand group in carbonatotetramminecobalt(III) ion has been recently investigated. A tracer technique utilizing radiocarbon was applied, and studies were made of the exchange kinetics,[4] the effect of ionic strength variation,[5] and the equilibrium isotope effect.[6] The present paper reports the results of a similar carbonate-exchange study of the ethylenediamine analog of the tetrammine complex. This aspect of the work was designed to provide evidence concerning the influence of type and structure of neutral ligand on the chemical reactivity of the complexed carbonate group. An additional approach is afforded by the occurrence of optically active forms of carbonato-bis-(ethylenediamine)-cobalt(III) salts. Comparison of exchange and racemization rate data enables conclusions as to the mechanism of the latter process, extending a technique suggested by early radioactive tracer studies of cobalt complexes.[7,8]

Experimental

A. **Preparation of Compounds.**—*trans*-Dichloro-bis-(ethylenediamine)-cobalt(III) chloride was prepared by the standard procedure.[9] It was converted to racemic carbonato-bis-(ethylenediamine)-cobalt(III) chloride by boiling for one hour with the calculated quantity of sodium carbonate in aqueous solution. The product was purified by fractional crystallization. Complete analysis yielded results in agreement with the formula $(\mathrm{Coen_2CO_3})\mathrm{Cl}$. Werner[10] has reported the existence of a monohydrate of this salt, but the water content of our product was negligible, nor did it show any deliquescent tendency.

Optically active *d*-$(\mathrm{Coen_2CO_3})\mathrm{Cl}$ was obtained by treating aqueous solution of *d*-$(\mathrm{Coen_2CO_3})_2\mathrm{CO_3}$, prepared by the method of Bailar and Peppard,[11] with slight excess of $\mathrm{BaCl_2}$. After standing overnight, the $\mathrm{BaCO_3}$ was filtered off and the *d*-$(\mathrm{Coen_2CO_3})\mathrm{Cl}$ precipitated by addition of alcohol and ether. The specific rotation, measured on a 0.1% solution at room temperature, was 740° in sodium-D light.

B. **Exchange Experiments.**—The experimental technique was only slightly modified from that previously described.[4] It was found that aqueous solutions of the en complex, with or without added carbonate, underwent small changes in *p*H and conductance on standing. These were complete within two or three hours at 50°, but required about 12 hours at room temperature. For example, at 50° a solution 0.01 *M* in complex and 0.0033 *M* in $\mathrm{Na_2CO_3}$ decreased in *p*H from 10.76 to 9.96 in three hours and changed only very slightly more on long standing. The conductance decreased by about 7% during the same three-hour interval to a constant value. Solutions of complex without added carbonate showed a similar *p*H behavior, but for these the conductance *increased* by about 10% to attain a constant value. The absorption spectrum of the solutions was determined over the range 3000–7000 Å. on a Hilger "Uvispek" photoelectric spectrophotometer. It exhibited only slight alteration during the *p*H and conductance readjustments. No doubt aquation equilibrations are involved in these processes (see Discussion). Consequently, in all the exchange work the solutions were allowed to stand overnight at reaction temperature before adding the final small portion of highly radioactive carbonate and commencing the exchange rate measurements.

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