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The polymer model of collagen degradation

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The mathematical description of polymer chain scission given by N. M. Emanuel' & D. C. Knorre (*Chemical Kinetics* (*Homogeneous Reactions*), John Wiley, New York, 1973) is shown to be inaccurate and an alternative formulation is presented. The model of collagen degradation proposed by T. E. Rudakova & G. E. Zaikov (*Polym. Deg. Stab.*, **18** (1987) 271) which is based upon the work of Emanuel' & Knorre is modified accordingly. The revised model is applied to the results of experiments on the effect of hydrolysis on collagen sutures and is found to fit the data only during the early stages of degradation. Possible causes of the lack of fit of the conceptual model are discussed.

INTRODUCTION

The abundance and structural properties of collagen has lead to a wide range of uses, including leathers, sutures and haemostatics. Understanding the mechanisms underlying the chemical degradation of collagen has importance for many of these applications. As part of a study, at the University of Newcastle upon Tyne, of the long-term survival of bone, investigations into the rate and pattern of collagen degradation are being undertaken. The first published model of collagen degradation known to the authors is that of Rudakova & Zaikov[1] who utilize the mathematical description of polymer chain scission given by Emanuel' & Knorre.[2] Attempts to use the model have revealed a flaw in this mathematical description. In this paper a revised mathematical formulation of chain scission, based on the assumptions made by Emanuel' & Knorre,[2] is presented. This is incorporated into the Rudakova & Zaikov model[1] which is then applied to data from experiments on collagen. The results indicate that the assumptions underlying the Rudakova & Zaikov model[1] are not valid during the entire degradation process and, consequently, that the model has a limited predictive capability.

THE POLYMER MODEL OF COLLAGEN DEGRADATION

The polymer model of the chemical degradation of collagen by hydrolysis proposed by Rudakova & Zaikov[1] is based on two hypotheses, the first of which relates to polymer chain scission in general and the second specifically to collagen weight loss. It is assumed that:

- hydrolysis is a first order reaction with respect to bond concentration such that the probability of hydrolysis at any site in the collagen α-chain is independent of the position of the bond in the chain;
- scission of the chain occurs until fragments achieve a critical length, whereupon they melt free from the triple helix.

The authors adopt a mathematical formulation of the model of chain scission based upon the first of these assumptions given by Emanuel' & Knorre.[2] The relationship between mean length P of polymer fragments at time t, the rate of reaction K, and the initial length of the polymer chain P_0 is given as:

$$-\ln \frac{P-1}{P} = -\ln \frac{P_0-1}{P_0} + Kt \qquad (1)$$

which can be rearranged to give:

$$P = \frac{P_0}{1+(P_0-1)\alpha} \qquad (2)$$

where $\alpha = 1 - \exp(-Kt)$ is the probability that a bond breaks by time t.

Emanuel' & Knorre[2] state the weight fraction, γ_x, of polymers x units long to be:

$$\gamma_x = \alpha \frac{x}{P}(1-\alpha)^{x-1}[2+(P-x-1)\alpha] \qquad (3)$$

Starting from eqns (1) and (3), Rudakova & Zaikov[1] derive an approximation for γ_x in a form which facilitates parameter identification. They assert that:

$$\gamma_x \approx 2xK^2t^2 \qquad (4)$$

and derive the total weight fraction, W_X, of polymers of length X or less using:

$$W_X = \sum_{x \leq X} \gamma_x \qquad (5)$$

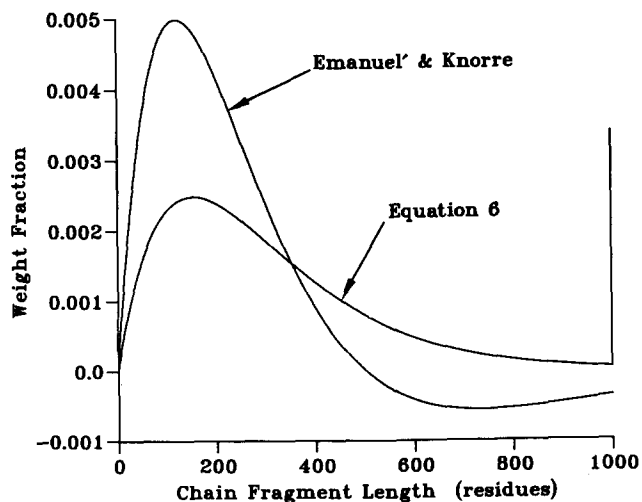thus invoking the second assumption that fragments of length less than or equal to a fixed

Fig. 1. Weight fraction of α-chain fragments of length x predicted by Emanuel' & Knorre[2] and by Eqn 6. $P_0 = 1000$ residues and $P = 150$ residues.

length X melt free from the collagen molecule. The fractional weight loss is given by W_X.

Equation (3) however, is not correct. This is demonstrated in Fig. 1 which shows the weight fraction of x-mers predicted by eqns (2) and (3) for a polymer chain of initial length 1000 units and with a mean degree of polymerisation of 150. Clearly, the negative values have no physical meaning. Figure 1 also shows the predicted weight fraction curve based on a revised mathematical formulation of polymer chain scission given by:

$$\gamma_x = \begin{cases} \alpha \dfrac{x}{P_0}(1-\alpha)^{x-1}[2+(P_0-x-1)\alpha] & \text{for } x < P_0 \\[2mm] (1-\alpha)^{P_0-1} & \text{for } x = P_0 \end{cases} \qquad (6)$$

A derivation of eqn (6) from the first assumption is given in the appendix. The mean degree of polymerisation represented in Fig. 1 is attained in the early stages of degradation $(Kt \approx 5\cdot7 \times 10^{-3})$ when a number of chains remain intact. The existence of these unbroken chains is indicated by the spike in the curve at $x = 1000$.

Figure 2 shows an example of the cumulative weight loss in collagen molecules over time, based on the Rudakova & Zaikov conceptual model.[1] Results are shown for the Emanuel' & Knorre formula, the Rudakova & Zaikov approximation to it, and for eqn (6).[1,2] In this example the initial chain length is 1000 units, the reaction rate 0·01 per unit time and the minimum melting length 30 residues. Given the validity of the conceptual model, it is clear from the figure that the application of eqn (3) to experimental data would lead to significant underestimates of the effective reaction rate constant K.

LIMITATIONS OF THE POLYMER MODEL

Okada et al.[3] and Rudakova & Zaikov[1] have investigated the chemical hydrolysis of collagen sutures by measuring the rate of weight loss. Figure 3 shows the polymer model (eqn (6)) applied to the weight loss data from Okada et al.[3] for untreated (Catgut-Plain-20) and tanned (Catgut-Chromic-20) sutures at pH 1·6 and at 37°C. In both cases the model can be made to
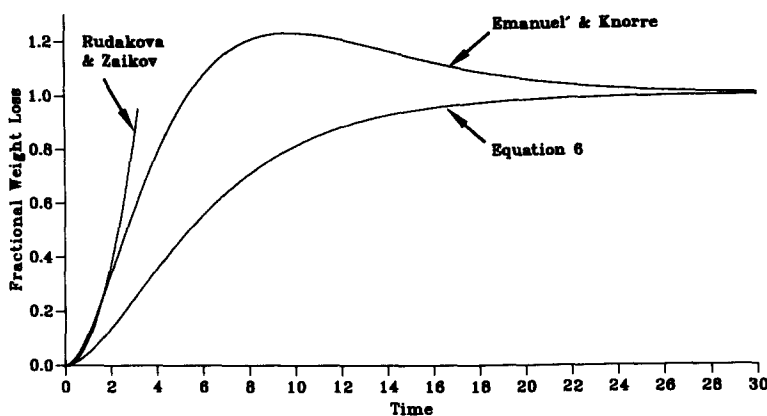
Fig. 2. Cumulative fractional weight loss predicted by Emanuel' & Knorre,[2] Rudakova & Zaikov[1] and Eqn 6. $P_0 = 1000$ residues, $K = 0.01$ per unit time and $X = 30$ residues.

fit the early weight loss data well, but it is not possible to use the same parameters to predict weight loss in the later stages of degradation.
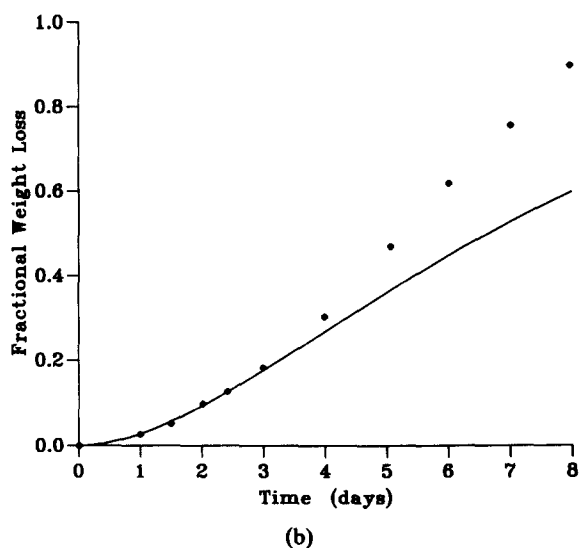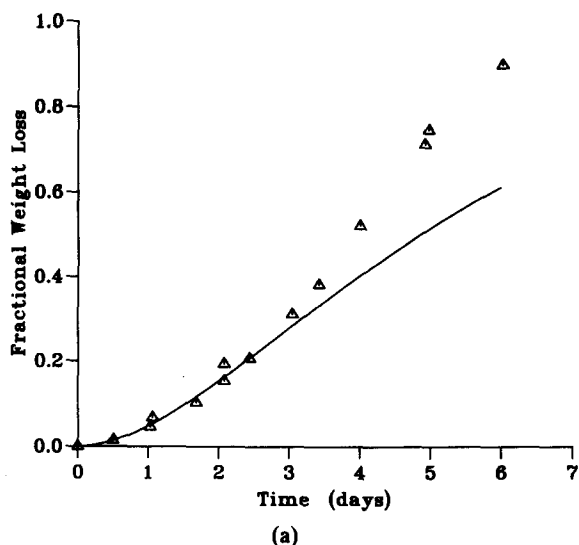

(a)

(b)

Fig. 3. Revised polymer model applied to weight loss data from Okada *et al.*[3] for sutures at pH 1·6 and at 37°C: (a) Catgut-Plain-20; (b) Catgut-Chromic-20.

Figure 4 shows data for collagen sutures at pH 2 and at 58·5°C taken from Rudakova & Zaikov[1] and shows a similar lack of fit.

The polymer model assumes that weight loss occurs when fragments achieve a critical melt length. However, collagen insolubility is a function of molecular interactions between adjacent polypeptide chains—principally hydrogen bonds between the three interwound strands of the triple helix and covalent cross-links within and between triple helices. In the polymer model, solubility is simply a function of fragment size, but in reality, weight loss will be governed by the extent to which inter-chain hydrogen bonds and cross-links prevent fragments from dissolving.

The use of a critical fragment size in the model suggests the existence of a weightless backbone from which smaller fragments melt free. The effect of this is less significant during the early
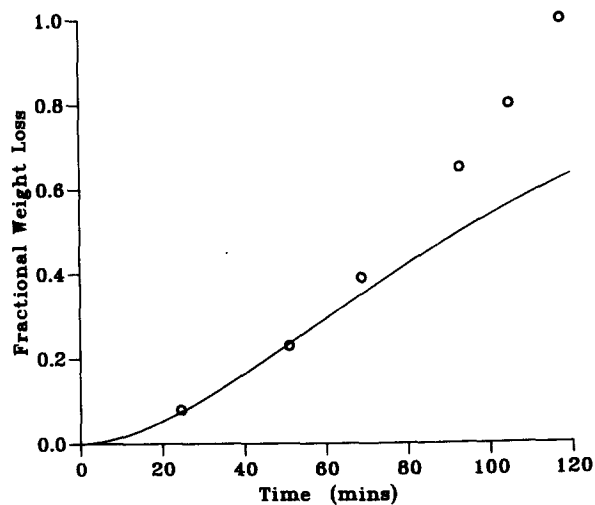

Fig. 4. Revised polymer model applied to weight loss data from Rudakova & Zaikov[1] for sutures at pH 2 and at 58·5°C.

stages of degradation when the great majority of the polymer complex remains intact, but even for the period in which the model can be made to fit the data, the nature of the relationship between the model parameter x and the actual lengths of fragments that melt free is unclear. The second assumption becomes increasingly inappropriate as degradation becomes more complete; there is no backbone from which to melt free, only a mutual interdependence of adjacent polymer fragments. As degradation proceeds the molecular interactions between adjacent polymers become weaker and, thus, dissolution of fragments occurs more readily. This is observed in the suture degradation studies as a more rapid weight loss of degraded collagen than is predicted by the polymer model.

REFERENCES

1. Rudakova, T. E. & Zaikov, G. E., *Polym. Deg. Stab.*, **18** (1987) 271.
2. Emanuel', N. M. & Knorre, D. G., *Chemical Kinetics* (*Homogeneous Reactions*) (translated from *Kurs Khim-icheskoi Kinetiki*) John Wiley, New York, 1973.
3. Okada, T., Hyashi, T. & Ikada, Y., *Biomaterials*, **13** (1992) 448.

APPENDIX

Let K be the rate of bond breakage due to hydrolysis in a polypeptide chain. Then the probability α that a given bond will break before time t is $1 - \exp(-Kt)$. Consider a large number of chains each containing P_0 basic units (amino acid residues). Then the weight fraction of x-mers, γ_x, is given by:

$$\gamma_x = \frac{\text{number of units in } x\text{-mers}}{\text{total numbers of units}} \quad \text{(A.1(a))}$$

As the number of units tends to infinity this expression tends to the probability that a unit chosen at random is part of an x-mer, and this may be written:

$$\sum_{i=1}^{P_0} P(u_i \text{ is part of an } x\text{-mer} \mid u_i \text{ is chosen})$$

$$\times P(u_i \text{ is chosen}) \quad \text{(A.1(b))}$$

where u_i is the ith unit from one end of the chain. If units are chosen at random:

$$P(u_i \text{ is chosen}) = \frac{1}{P_0} \quad \text{(A.1(c))}$$

Equations (A.1(a), (b) and (c)) provide the basis for calculating γ_x.

It is useful to consider three cases. First the case in which $x \leq P_0/2$. If the unit chosen is at the left hand end of the chain (i.e. $i = 1$) then it is part of an x-mer if the xth bond from the end is broken and the first $x - 1$ remain intact. The probability that this occurs is:

$$\alpha(1 - \alpha)^{x-1} \quad \text{(A.2)}$$

If the chosen unit is greater than x positions from the end of the chain then it is part of an x-mer if it belongs to a sub-chain in which two end bonds are broken and the intervening $x - 1$ are intact. Since there are x such sub-chains containing the chosen unit, the probability that the unit is part of an x-mer is:

$$x\alpha^2(1 - \alpha)^{x-1} \quad \text{(A.3)}$$

If the unit chosen is within x positions of the end of the chain, then one of the x-mers containing the unit includes the end unit of the chain and $i - 1$ do not. Thus, the probability that it is part of an x-mer is:

$$\alpha(1 - \alpha)^{x-1} + (i - 1)\alpha^2(1 - \alpha)^{x-1} \quad \text{(A.4)}$$

Substituting eqns (A.3) and (A.4) into eqns (A.1(a), (b) and (c)), remembering that eqn (A.4) applies at both ends of the chain, gives:

$$\gamma_x = \left(2 \sum_{i=1}^{x} \alpha(1 - \alpha)^{x-1}\{1 + (i - 1)\alpha\}\right.$$

$$\left. + \sum_{i=x+1}^{P_0-x} x\alpha^2(1 - \alpha)^{x-1}\right) \frac{1}{P_0} \quad \text{(A.5)}$$

for

$$x \leq \frac{P_0}{2}$$

In the second case $P_0/2 < x < P_0$. If the unit chosen at random is within $P_0 - x$ positions from the left hand end of the chain, then the probability that it is part of an x-mer is given by eqn (A.4). If the unit is elsewhere in the chain then two of the x-mers containing it will contain units at the end of the chain, and $P_0 - x - 1$

x-mers will contain no end units. Thus, the probability that the unit is part of an *x*-mer is

$$2\alpha(1 - \alpha)^{x-1} + (P_0 - x - 1)\alpha^2(1 - \alpha)^{x-1} \quad \text{(A.6)}$$

Substituting eqns (A.4) and (A.6) into eqns (A.1(a), (b) and (c)) gives

$$\gamma_x = \left(2 \sum_{i=1}^{P_0-x} \alpha(1 - \alpha)^{x-1}\{1 + (i - 1)\alpha\}\right.$$

$$\left. + \sum_{i=P_0-x+1}^{x} \alpha(1 - \alpha)^{x-1}\{2 + (P_0 - x - 1)\alpha\}\right) \frac{1}{P_0}$$

$$\text{for } \frac{P_0}{2} < x < P_0 \quad \text{(A.7)}$$

Both eqns (A.5) and (A.7) simplify to give the same expression:

$$\gamma_x = \alpha \frac{x}{P_0}(1 - \alpha)^{x-1}\{2 + (P_0 - x - 1)\alpha\}$$

$$\text{for } x < P_0 \quad \text{(A.8)}$$

Finally, if $x = P_0$ then a chosen unit is part of an *x*-mer if all bonds in the chain remain unbroken and so the probability that it is part of an *x*-mer is given by

$$(1 - \alpha)^{P_0-1} \quad \text{(A.9)}$$

Substituting eqn (A.9) into eqns (A.1(a), (b) and (c)) gives

$$\gamma_{P_0} = (1 - \alpha)^{P_0-1} \quad \text{(A.10)}$$

Equations (A.8) and (A.10) together give the final result

$$\gamma_x = \begin{cases} \alpha \dfrac{x}{P_0}(1 - \alpha)^{x-1}\{2 + (P_0 - x - 1)\alpha\} & \text{for } x < P_0 \\[2mm] (1 - \alpha)^{P_0-1} & \text{for } x = P_0 \end{cases}$$

$$\text{(A.11)}$$