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Equilibrium Ratio of Polymers to Monomers in Cooperative Polymerization of Amyloid-β Protein

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Equilibrium Ratio of Polymers to Monomers in Cooperative Polymerization of Amyloid-β Protein

Abstract

Amyloid-β42 is a protein polymer that catalyzes the formation of pathogenic amyloid plaques that are a prominent feature in the brain tissue of patients who suffer from Alzheimer's disease. Aβ42 polymerizes via a nucleation-elongation mechanism; several monomers must first congregate into a nucleus before it can elongate into a polymer. The nucleation step is energetically unfavorable since a nucleus smaller than 7 to 8 monomeric units is unstable, therefore the pieces tend to dissociate faster than they can bond together. A solution of Aβ42 will consist of 100% monomers and oligomers smaller than the nucleus when the total concentration is below the critical level. However, once the concentration of free monomers meets the critical level, polymerization can happen spontaneously and there is a sharp increase in the percentage of polymers at equilibrium. This mechanism, also known as cooperative polymerization, can be understood by simplifying the polymer concentrations as terms of a geometric series. Having a better understanding of the thermodynamic and kinetic properties of Aβ42 polymerization can be very useful in finding a way to control the accumulation of amyloid fibrils in Alzheimer's patients.

Keywords

Alzheimer's disease, Amyloid-β42, protein polymer, monomer, oligomer, equilibrium ratio, polymerization, brain tissue, peptide fibrils, nucleation, mathematical induction, geometric series, Koebe function

PROBLEM STATEMENT

Amyloid-β(1-42) is a protein polymer that has been implicated as a causal factor in Alzheimer's disease, as it is suspected of seeding the aggregation of amyloid plaques in brain tissue. The polymerization of Aβ42 begins with the nucleation of 7 to 8 monomers, which is energetically unfavorable since it is unstable.[Lee] Once nucleation is achieved, further elongation of the polymer is much easier since there is more molecular surface area available for interactions between units. This method of polymerization is called cooperative polymerization, and in an effort to better understand how Aβ42 propagates in human tissue, it is useful to be able to calculate the ratio of polymers to monomers of Aβ42 at equilibrium.

Describe how to find the equilibrium ratio of polymerized vs. monomeric Aβ42 resulting from the cooperative polymerization of Aβ42 peptide into long chains.

MOTIVATION

Amyloid-β(1-42) peptide has been implicated as having a causal relationship to Alzheimer's Disease, as it has been shown to be involved in the formation and accumulation of Amyloid-β plaques in brain tissue.[Novo, Cohen] Amyloid-β(1-42) peptide is a long fibrillar protein composed of 42 monomeric subunits (amino acids). Research has shown that the polymerization of Aβ42 peptide exhibits a cooperative behavior, in which elongation of the fibril occurs after an initial nucleation step.[Novo, Cohen] A peptide that undergoes cooperative polymerization will not begin to form polymers until a critical aggregation concentration c_c has been reached.[Novo, Cohen, Zhao] Nearly all molecules in solution will exist as monomers while the total concentration of monomers c_t is less than the critical aggregation constant c_c.[Zhao] Once the total concentration of monomer c_t in solution is equal to this critical aggregation concentration, c_c, there is typically an abrupt change in the equilibrium ratio of monomers to polymers, as there is a sudden increase in the number of polymers and the concentration of monomers stays the same regardless of how much more monomers are added to solution after the critical point c_c.[Novo, Cohen, Zhao]

Understanding the thermodynamics and kinetics that underlie the cooperative polymerization mechanism of Aβ42 could be very useful in finding a way to prevent and treat the formation and accumulation of amyloid aggregates that are found to be a characteristic histopathological component in Alzheimer's Disease.

MATHEMATICAL DESCRIPTION AND SOLUTION APPROACH

To calculate the equilibrium ratio, we consider that the equilibrium concentrations of polymers of increasing degrees follow a pattern such that they become terms of a geometric series. The total concentration of all monomers c_t is then equal to the sum of this geometric series (equation 26). The degree of polymerization in terms of average chain length can also be calculated as the ratio of c_t over the total concentration of products (equation 31). Slightly different versions of these two equations can be combined in such a way to approximate the equilibrium concentration of Aβ42 monomers when $c_t > c_c$ and we assume a small nucleation factor of $\sigma = 0.01$. For a total concentration c_t that is slightly above c_c and average chain lengths of 42 subunits, the equilibrium ratio of polymers to monomers is shown to be 17.639, with c_t at 94.63% polymers and 5.36% monomers of Aβ42. These results are consistent with what is to be expected of a cooperative polymerization above the critical concentration.

The polymerization of peptide fibrils such as Aβ42 starts with an initial nucleation, which can be simplified here as the dimerization of two monomers A + A → A_2 (equation 1).[Zhao] Actual data shows that the nucleus of Aβ42 polymerization consists of about 7 to 8 monomeric residues.[Lee] Figure 1 illustrates the elongation of a polymer following an initial nucleation event.[Zhao] The equilibrium constant K is the ratio of the concentration of products over the concentration of reactants at equilibrium (equations 1-4).[Zhao] $[A_i]$ is the concentration of the i^{th} degree polymers. [A] is the concentration of monomers. The rate constants k_i and k_{-i} quantify the rate of the forward and reverse reactions for adding or cleaving a monomer subunit from an existing nucleus, respectively.[Zhao]

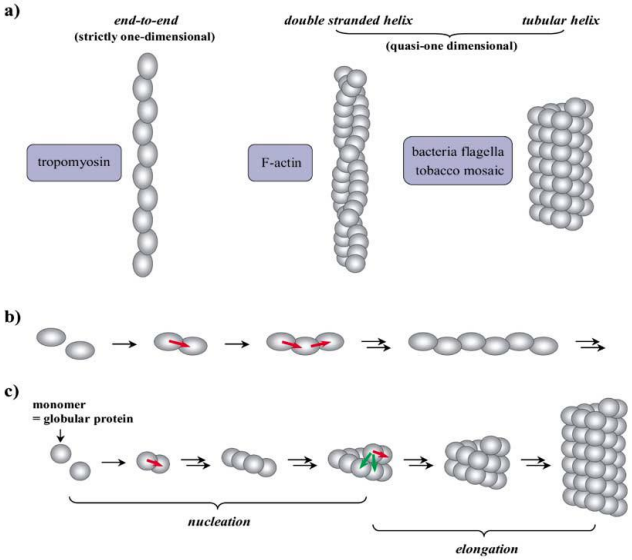

Figure 1 [Zhao & Moore]
(a) Representations of fibrillar polymers. Tropomyosin is an example of a linear polymer while F-actin and tobacco mosaic virus are examples of helical and tubular polymers, respectively.[Zhao]
(b) Elongation of a linear polymer.
(c) Nucleation followed by elongation of a polymer that exhibits cooperative polymerization. The red arrows represent covalent bonds that form between monomers. Green arrows represent non-covalent interactions between neighboring monomers. These non-covalent interactions make elongation of the polymer much more energetically favorable thus easier than the nucleation.[Zhao]

Equations (4), (8), (12), (23), and (25) below are based on mathematical induction.

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$A + A \leftrightarrow A_2$ $K_2 = k_2/k_{-2} = [A_2]/[A]^2$ (1)

$A_2 + A \leftrightarrow A_3$ $K_3 = k_3/k_{-3} = [A_3]/[A][A_2]$ (2)

$A_3 + A \leftrightarrow A_4$ $K_4 = k_4/k_{-4} = [A_4]/[A][A_3]$ (3)

$A_{i-1} + A \leftrightarrow A_i$ $K_i = k_i/k_{-i} = [A_i]/[A][A_{i-1}]$ (4)

The rate equations 1-4 can be rearranged to give the concentration of polymers at equilibrium, as shown below in equations 5-8.[Zhao]

$[A_2] = K_2[A]^2$ (5)

$[A_3] = K_3[A_2][A] = K_3K_2[A]^3$ (6)

$[A_4] = K_4[A_3][A] = K_4K_3K_2[A]^4$ (7)

$[A_i] = K_i[A_{i-1}][A] = K_i \ldots K_3K_2[A]^i$ (8)

For a hypothetical model in which there is a single nucleation step followed by elongation of the polymer, the first nucleation step (equation 1) is energetically less favorable than the following elongation steps.[Zhao] Each of the elongation steps following nucleation can be thought of as requiring the same amount of energy, which is much less than the nucleation reaction, so $K_2 < K_3 = \ldots = K_i = \ldots = K$.[Zhao] Therefore, equations 5-8 can be modified into the following equations 9-12.[Zhao]

$[A_2] = K_2[A]^2$ (9)

$[A_3] = K[A_2][A] = KK_2[A]^3$ (10)

$[A_4] = K[A_3][A] = K^2K_2[A]^4$ (11)

$[A_i] = K[A_{i-1}][A] = K^{i-2}K_2[A]^i$ (12)

It turns out that equations 9-12 are terms of a geometric series, in which the first term $a = K_2[A]^2$, and the common ratio $r = K[A]$.

The nucleus for Aβ42 polymerization has been experimentally estimated to be 7 to 8 monomeric subunits in length.[Lee] In this case, the first 7 or 8 steps would be the nucleation steps and each step afterwards would be an energetically more favorable elongation step, and $K_2 \approx K_3 \approx \ldots K_7 \approx K_8 < K_9 = K_{10} = K_{11} = \ldots K_i = K$. Therefore, the equilibrium concentrations for the oligomers of Aβ42 might be better approximated by

equations 13-23. After the 8th step, these too become terms of a geometric series, with the first term a = $K_8K_7K_6K_5K_4K_3K_2[A]^9$ and common ratio r = K[A].

$[A_2] = K_2[A]^2$ (13)

$[A_3] = K_3K_2[A]^3$ (14)

$[A_4] = K_4K_3K_2[A]^4$ (15)

$[A_5] = K_5K_4K_3K_2[A]^5$ (16)

$[A_6] = K_6K_5K_4K_3K_2[A]^6$ (17)

$[A_7] = K_7K_6K_5K_4K_3K_2[A]^7$ (18)

$[A_8] = K_8K_7K_6K_5K_4K_3K_2[A]^8$ (19)

$[A_9] = K_8K_7K_6K_5K_4K_3K_2K[A]^9$ (20)

$[A_{10}] = K_8K_7K_6K_5K_4K_3K_2K^2[A]^{10}$ (21)

$[A_{11}] = K_8K_7K_6K_5K_4K_3K_2K^3[A]^{11}$ (22)

$[A_i] = K_8K_7K_6K_5K_4K_3K_2K^{i-8}[A]^i \quad (i \geq 8)$ (23)

The nucleation factor σ is the ratio of the nucleation equilibrium constant K_2 over the elongation equilibrium constant K (equation 24).[Zhao] A small value for σ means that there is a steep barrier for the first nucleation step, meaning that the polymerization of that particular polymer exhibits a high level of cooperativity.[Muschol]

$\sigma = K_2/K$ (24)

Combining equations 12 and 24, equation 25 can be derived for calculating the concentration of the polymer $[A_i]$.[Zhao] K^{-1} is the dissociation constant, which is the reverse of K.

$[A_i] = K[A_{i-1}][A] = K^{i-2}K_2[A]^i = \sigma K^{-1}(K[A])^i \quad (i \geq 2)$ (25)

c_t is the total concentration of monomers in solution, which includes both free monomers and monomers that are bound in polymers.[Muschol] c_t is the amount of monomers that are put into solution and it is the independent variable that is controlled by the experimenter. For polymers that exhibit cooperative polymerization, such as Aβ42, when the total

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monomer concentration c_t reaches the critical aggregation concentration c_c, there is a sudden increase in the number of polymers. As more monomers are added to solution, c_t becomes higher than c_c and the number of polymers continues to increase while the number of monomers stays the same. The critical aggregation concentration c_c is equal to the dissociation constant K^{-1}. When c_t is below c_c, no polymerization takes place and virtually all of the molecules in solution exist in the monomeric form.[Zhao, Novo] What actually happens is that monomers are always randomly associating and dissociating in solution, but because dimers are much less stable than monomers, the tendency is for the dimers to dissociate before further elongation can take place. However, once c_c is reached the barrier to nucleation is overcome and the elongation is much easier.[Zhao] The formula for c_t is given in equation 26 [Zhao] :

$$c_t = \sum_{i=1}^{\infty} i[Ai] \quad ([A_1] = [A]) \quad (26)$$

Because the equilibrium concentrations of the polymers are the terms of a geometric series, an equation can be derived which uses this geometric series to solve for c_t (equation 27).[Zhao] More detailed calculations for deriving equation 27 are found in the Appendix.

$$c_t = [A] + \sum_{i=2}^{\infty} i\sigma K^{-1}(K[A])^i = (1-\sigma)[A] + \frac{\sigma[A]}{(1-K[A])^2} \qquad (27)$$

Figure 2 illustrates how the percent concentration of monomers $[A]/c_t$ decreases as the total concentration c_t increases.[Zhao] For a polymer that exhibits highly cooperative polymerization, such as Aβ42, the nucleation factor σ will be small. If it can be assumed that Aβ42 has a nucleation factor of $\sigma = 0.0001$, then the solution will consist of nearly 100 percent monomers up until c_t reaches the critical concentration c_c. Once c_t reaches c_c, there is a steep decline in the percentage of monomers and a dramatic increase in the number of polymers. The x-coordinate of the graph in Figure 2 is the equilibrium constant K times c_t. When c_t equals c_c, which is equal to the dissociation constant K^{-1}, $Kc_t = 1$. It can be seen in Figure 2 that when $Kc_t=1$, the tangent line to the slope at this point is nearly vertical as the function decreases. This means that for a solution of Aβ42 at or above the critical concentration c_c, its ratio of polymers to monomers at equilibrium will be quite large. Most of the molecules will exist as oligomers and longer chains of Aβ42. A large value for σ, such as 0.9, implies that the polymer does not undergo cooperative polymerization but instead follows an isodesmic mechanism of polymerization, and its percentage concentration of monomers decreases more gradually as a function of Kc_t.[Zhao]

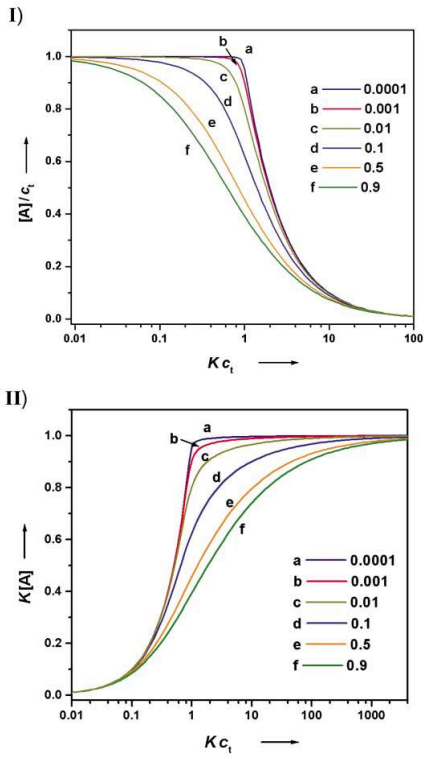

Figure 2 [Zhao & Moore]
(top) The percentage of monomer [A]/c_t as a function of total concentration Kc_t.

(bottom) The concentration of monomers K[A] in solution as a function of Kc_t. K[A] continues to increase as more monomers are added to solution, until the point at which c_t reaches the critical concentration c_c. At that point, the concentration of monomers stays the same for a polymer that undergoes cooperative polymerization.

In this diagram, a through f represent the different values of the nucleation factor, σ. A polymer type that exhibits cooperative polymerization will have a small σ, while a polymer type that follows an isodesmic model of polymerization will have a large σ.

c_p is the total concentration of all products, including monomers, oligomers, and polymers of varying degrees of polymerization.[Zhao] The formula for c_p is given in equation 28 [Zhao] :

$$c_p = \sum_{i=1}^{\infty} [A_i] \quad ([A_1] = [A]) \qquad (28)$$

Using formula (25) $[A_i] = \sigma K^{-1}(K[A])^i$ in (28) to substitute for $[A_i]$ for $i \geq 2$ we obtain equation 29 [Zhao] :

$$c_p = \sum_{i=1}^{\infty} \sigma K^{-1}(K[A])^i + (1-\sigma)[A] \qquad (29)$$

Formula 29 for c_p can be simplified to equation 30 (see the Appendix):

$$c_p = (1-\sigma)[A] + \frac{\sigma[A]}{1-K[A]} \qquad (30)$$

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The degree of polymerization in terms of average lengths of polymers, $<dp>_n$, can be found using the formula in equation 31.[Zhao] Detailed calculations that explain how equation 31 is derived can be found in the Appendix.

$$< dp >_n = \frac{c_t}{c_p} = \frac{[A] + \sum_{i=2}^{\infty} i[A_i]}{[A] + \sum_{i=2}^{\infty} [A_i]} = \frac{\sigma + (1-\sigma)(1-K[A])^2}{\sigma(1-K[A]) + (1-\sigma)(1-K[A])^2} \tag{31}$$

The degree of polymerization in terms of average weight of the polymers $<dp>_w$ is given by equation 32.[Zhao] Detailed calculations can be found in the Appendix.

$$< dp >_w = \frac{[A] + \sum_{i=2}^{\infty} i^2[A_i]}{[A] + \sum_{i=2}^{\infty} i[A_i]} = \frac{\sigma(1+K[A]) + (1-\sigma)(1-K[A])^3}{\sigma(1-K[A]) + (1-\sigma)(1-K[A])^3} \tag{32}$$

Figure 3 illustrates how both $<dp>_n$ and $<dp>_w$ increase as Kc_t increases.[Zhao] If the polymerization of Aβ42 has a nucleation factor of $\sigma = 0.0001$, then there is an abrupt increase in both $<dp>_n$ and $<dp>_w$ when $c_t = c_c$. The critical concentration c_c occurs at $Kc_t = 1$, since at critical concentration $c_t = c_c = K^{-1}$, and $KK^{-1}=1$. When $Kc_t < 1$, virtually all of the total concentration c_t in solution exists as monomers. The moment $c_t = c_c$, however, there is a sudden increase in the lengths of the polymers, $<dp>_n$ and an even steeper increase in the average weights of the polymers, $<dp>_w$.[Zhao] As a result, Aβ42 will have longer chains and heavier polymers at equilibrium as the total concentration c_t reaches c_c and increases above.

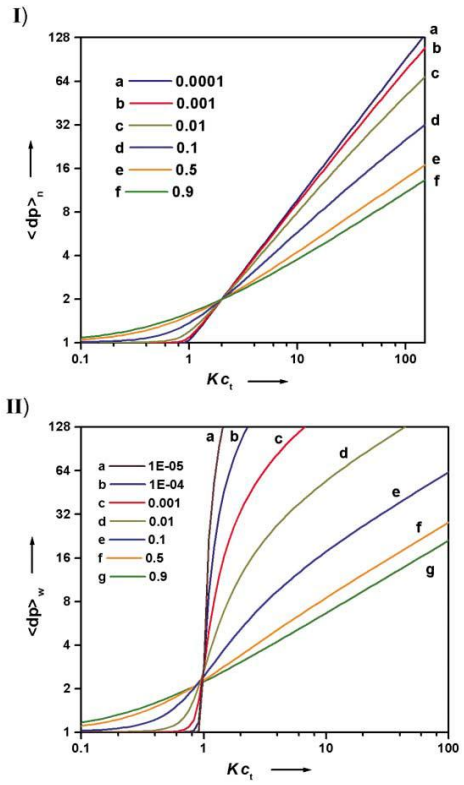

Figure 3 [Zhao & Moore]
(top) The average length of polymers $<dp>_n$ as a function of Kc_t.

(bottom) The average weight of polymers $<dp>_w$ as a function of Kc_t.

a-f represent different values for the nucleation factor, σ. A small value for σ occurs for cooperative polymerization, and a large value for σ occurs for isodesmic polymerization.

Since the cooperative polymerization of Aβ42 starts with a nucleus of about 7-8 monomeric units before it can elongate, which is more complicated than a simple dimer, the formulas to find its parameters at equilibrium are a little different.[Lee, Zhao] Equation 33 gives an approximation for the total concentration c_t in terms of [A], σ, and K[A].[Zhao]

$$c_t \approx [A] + \frac{\sigma[A]}{(1-K[A])^2} \qquad (33)$$

An approximation of the degree of polymerization in terms of average chain length of the polymers for a polymer such as Aβ42 that undergoes multiple nucleation steps is given by equation 34.[Zhao]

$$< dp >_n = \frac{\sum_{i=n}^{\infty} i[A_i]}{\sum_{i=n}^{\infty} [A_i]} \approx \frac{1}{1-K[A]} \approx \left(\frac{c_t - c_c}{c_c}\right)\sigma^{\frac{-1}{2}} \qquad (34)$$

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DISCUSSION

Although the chain length of Aβ42 is 42 monomers long, at the moment when $c_t = c_c$, the degree of polymerization in terms of average length may be around 9 or 10, since the nucleus is about 7 to 8 monomers long, so at the instant when $c_t = c_c$, $<dp>_n$ may be assumed to be approximately 9. Using this data for equation 34 yields the following result (equations 35 and 36).

$$< dp >_n = 9 \approx \frac{1}{1 - K[A]} \qquad (35)$$

$$1 - K[A] \approx \frac{1}{9} \qquad (36)$$

Assuming that the nucleation factor $\sigma = 0.0001$ and substituting $1 - K[A] = 1/9$ into equation 33, the concentration of monomers [A] at equilibrium when c_t reaches the critical concentration c_c is solved in equations 37-40. Experiments show that the critical concentration for Aβ42 polymerization is $c_c = 50 \times 10^{-6} M$.[Tjernberg]

$$c_t = c_c = 50 \times 10^{-6} M \approx [A] + \frac{0.0001[A]}{\left(\frac{1}{9}\right)^2} \qquad (37)$$

$$50 \times 10^{-6} M \approx [A] + (0.0001)9^2[A] \qquad (38)$$

$$50 \times 10^{-6} M \approx 1.0081[A] \qquad (39)$$

$$[A] \approx 49.598 \times 10^{-6} M \qquad (40)$$

This result is counterintuitive. An equilibrium concentration of the monomer [A]=49.598 $\times 10^{-6}$M would mean that the equilibrium concentration of the polymer $[A_i]$ =0.402 $\times 10^{-6}$M, which is much less than that of the monomer. This should not happen for a polymerization with a very small nucleation factor; the concentration of polymers is supposed to increase dramatically at the instant when $c_t = c_c$.

If instead we consider an average chain length of $<dp>_n = 42$ and a larger value of the nucleation factor, $\sigma = 0.01$, we can get values for [A] and $[A_i]$ that more closely meet the objective. Since it requires a higher total concentration c_t to achieve the full lengths of the Aβ42 polymers, c_t must be greater than c_c. Let us assume that $c_t = 60 \times 10^{-6}$M. Equations 41 to 46 show the calculations. In this case, [A] =3.219$\times 10^{-6}$M and $[A_i]$ =56.781$\times 10^{-6}$M, which gives an equilibrium ratio of polymer to monomers of 17.639 (equation 47). The products in this case would be 94.63% polymers and 5.36% monomers. This result is much closer to what is expected for a cooperative polymerization. However, in order to

get this result, we chose a larger nucleation factor σ. Using equation 33 to find [A], it turns out that a smaller value of σ actually gives a larger value of [A], which is the opposite of what is supposed to happen for a highly cooperative polymerization. Nevertheless, a value of σ = 0.01 is still small and would be considered appropriate for a cooperative polymerization. The exact value of σ for Aβ42 could not be found in the literature.

$$60\times10^{-6}M\approx[A]+\frac{0.01[A]}{\left(\frac{1}{42}\right)^2} \tag{41}$$

$$60\times10^{-6}M\approx[A]+0.01(42^2)[A] \tag{42}$$

$$60\times10^{-6}M\approx[A]+17.64[A] \tag{43}$$

$$60\times10^{-6}M\approx18.64[A] \tag{44}$$

$$[A]\approx 3.219\times10^{-6}\text{M} \tag{45}$$

$$[A_i]=60\times10^{-6}\text{M}-[A]=56.781\times10^{-6}\text{M} \tag{46}$$

$$\frac{[A_i]}{[A]}=\frac{56.781\times10^{-6}M}{3.219\times10^{-6}M}=17.639 \tag{47}$$

The implications of these results can be useful as it can be applied towards the ongoing research for treatment and possible cure for Alzheimer's Disease. Amyloid aggregates are also implicated in Parkinson's Disease, Type II diabetes, and rheumatoid arthritis.[Mulaj] Understanding the mechanism of Aβ42 polymerization, which requires having knowledge of the thermodynamic and kinetic properties of its nucleation and elongation steps, can lead to finding a way to control the formation of Aβ42 aggregates in human tissue. Pharmaceuticals can be developed to counter-act against pathogenic amyloid formations, and in order to find the correct dosage, for example, it is useful to know the equilibrium concentrations of Aβ42 oligomers in the body under specific circumstances.

CONCLUSIONS AND RECOMMENDATIONS

A polymer such as Aβ42 that undergoes cooperative polymerization begins with a nucleation process that is energetically unfavorable because there are less monomers within the nucleus to interact with incoming monomers. The monomers of the nucleus tend to dissociate from each other before the nucleus has a chance to grow further. Before

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c_t reaches the critical concentration c_c, the rate of dissociation k_{-i} is faster than the rate of association k_i, and nearly 100% of the amino acids within the solution exist as monomers.[Zhao] For a cooperative polymer such as Aβ42, once $c_t = c_c$, there is a sharp increase in the amount of polymers in solution, and as c_t continues to increase, the ratio of polymers to monomers at equilibrium becomes greater and at some point at which $c_t > c_c$, the percentage of monomers in the solutions stays the same while the amount of polymers will continue to increase as more monomers are added to solution.[Zhao] The steep curve that represents the sharp increase of polymers at c_c can be likened to what happens during a standard phase transition.[Muschol] When $c_t < c_c$, even by the smallest amount, 100% of the amino acids are in the form of monomers. Once $c_t = c_c$ there is a dramatic reversal as the majority of products at equilibrium will be polymers. This is very different from the gradual change that occurs for a polymer that does not undergo a cooperative mechanism.

A few assumptions had to be made in order to calculate the ratio of polymers to monomers at equilibrium for Aβ42. Data for the cooperative polymerization of Aβ42 was hard to come by, as it is difficult to measure the concentrations of aggregated amyloid vs. monomers at equilibrium. The reactions occur very slowly, so it takes a long time before equilibrium is reached.[Muschol] So even though there is a sharp increase in polymers when $c_t = c_c$, this change is not seen until the reaction reaches equilibrium and that takes some time. Polymerizations that start with a dimer are simpler to study but rarely occur in nature, and the nucleus of Aβ42 consists of 7-8 monomers.[Lee, Muschol] Because of its greater nucleus size, there are multiple rate-limiting steps during nucleation, so what actually happens in nature is a bit more complicated than what simple mathematical models try to represent.[Muschol] What can be studied *in vitro* in the lab has its limitations, yet these mathematical models still provide critical insight into how and why cooperative polymerization is observed.[Muschol]

The critical concentration $c_c = 50 \times 10^{-6}$ M for Aβ42 polymerization, and at full length an Aβ42 polymer consists of 42 monomeric units.[Tjernberg] Using this data along with the assumption of $\sigma = 0.01$, when c_t is slightly above c_c (we used another assumption, $c_t = 60 \times 10^{-6}$M), the concentrations at equilibrium were found to be [A]=3.219×10^{-6}M and $[A_i]$ =56.781×10^{-6}M. This gives an equilibrium ratio of $\frac{[A_i]}{[A]} = 17.639$. At equilibrium, c_t is 94.63% polymers and 5.36% monomers. This seems very reasonable for a cooperative polymerization.

However, a larger value of σ actually gave a smaller value for [A] when using equation 33 to find [A]. This is problematic, since the smaller the value of σ the more highly cooperative the polymerization, and a highly cooperative polymerization should produce a higher percentage of polymers when $c_t \geq c_c$. It would help to have more available data for Aβ42 polymerization and maybe even improved approximations for the equilibrium concentration formulas.

As a suggestion, it might be worthwhile to use a computer simulation to study the cooperative polymerization of Aβ42 since it is difficult to measure the concentrations of

polymers vs. monomers at equilibrium experimentally. Software such as Autodesk Maya could possibly create an animated 3-dimensional replication of Aβ42 polymerization, which might help to study its thermodynamic properties in a way that has not yet been accomplished in a traditional laboratory.

NOMENCLATURE

Symbol	Description	Units
c_t	Total concentration of monomers (includes both free monomers and those bound within a polymer)	M = mol/L
c_c	Critical aggregation concentration	M = mol/L
k_i	Rate constant for forward reaction (monomer addition)	$M^{-1}s^{-1}$
k_{-i}	Rate constant for reverse reaction (monomer dissociation)	$M^{-1}s^{-1}$
K	Equilibrium constant (ratio of product concentration over reactant concentration)	Unit-less constant
K^{-1}	Dissociation constant (ratio of reactant concentration over product concentration)	Unit-less constant
σ	Nucleation factor (K_2/K)	Unit-less constant
[A]	Concentration of monomers	M
$[A_i]$	Concentration of polymers	M
i	Degree of polymerization	No unit
c_p	Total concentration of all products, including monomers, oligomers, and polymers	M
$<dp>_n$	Degree of polymerization in terms of average length of the polymers (average number of monomer units in chain)	Unit-less
$<dp>_w$	Degree of polymerization in terms of average weight	Unit-less

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APPENDIX

Below are the more detailed calculations on how to derive equation 27 for c_t:

$$c_t = [A] + \sum_{i=2}^{\infty} i\sigma K^{-1}(K[A])^i = (1-\sigma)[A] + \frac{\sigma[A]}{(1-K[A])^2}$$

Based on the Maclaurin series (equation I), this series in terms of z is differentiated (equation II) in order to obtain equation III. Both sides of equation III are multiplied by z to get equation IV, which is known as the Koebe function.[Grinshpan] For this Koebe function, z = K[A] and n=*i*. Substituting these values gives equation V.

$$\frac{1}{1-z} = \sum_{n=0}^{\infty} z^n \qquad \text{(I)}$$

$$\frac{d}{dz}\left(\frac{1}{1-z}\right) = \frac{d}{dz}\sum_{n=0}^{\infty} z^n \qquad \text{(II)}$$

$$\frac{1}{(1-z)^2} = \sum_{n=1}^{\infty} n z^{n-1} \qquad \text{(III)}$$

$$\frac{z}{(1-z)^2} = \sum_{n=1}^{\infty} n z^n \qquad \text{(IV)}$$

$$\frac{K[A]}{(1-K[A])^2} = \sum_{i=1}^{\infty} i(K[A])^i \qquad \text{(V)}$$

Equation 26 gives the formula to find c_t:

$$c_t = \sum_{i=1}^{\infty} i[Ai] \quad ([A_1] = [A])$$

Equation 25 showed that $[A_i] = \sigma K^{-1}(K[A])^i$:

$[A_i] = K[A_{i-1}][A] = K^{i-2}K_2[A]^i = \sigma K^{-1}(K[A])^i \qquad (i \geq 2)$

So the formula for c_t becomes equation VI:

$$c_t = \sum_{i=1}^{\infty} i\sigma K^{-1}(K[A])^i + (1-\sigma)[A] \qquad \text{(VI)}$$

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The first term of this series, [A], can be drawn to obtain equation VII:

$$c_t = [A] + \sum_{i=2}^{\infty} i\sigma K^{-1}(K[A])^i \qquad \text{(VII)}$$

Because σ and K^{-1} are both constants, according to Theorem 8.2.8 they can be placed in front of the infinite series (equation VIII).[Stewart] The first term of the series is K[A], so the sum of the series from 1 to infinity minus the first term K[A] is equal to the sum of the series from 2 to infinity (equation IX). Substituting the Koebe function (equation V) into equation IX gives equation X. σK^{-1} is then distributed to the terms within the bracket (equation XI) and K^{-1} times K gives 1, so those cancel (equation XII). Combining like terms gives equation 27.

$$c_t = [A] + \sigma K^{-1} \sum_{i=2}^{\infty} i(K[A])^i \qquad \text{(VIII)}$$

$$c_t = [A] + \sigma K^{-1} \left[\sum_{i=1}^{\infty} i(K[A])^i - K[A] \right] \qquad \text{(IX)}$$

$$c_t = [A] + \sigma K^{-1} \left[\frac{K[A]}{(1-K[A])^2} - K[A] \right] \qquad \text{(X)}$$

$$c_t = [A] + \frac{\sigma K^{-1} K[A]}{(1-K[A])^2} - \sigma K^{-1} K[A] \qquad \text{(XI)}$$

$$c_t = [A] + \frac{\sigma[A]}{(1-K[A])^2} - \sigma[A] \qquad \text{(XII)}$$

Hence equation 27 follows: $c_t = (1-\sigma)[A] + \frac{\sigma[A]}{(1-K[A])^2}$

Below are the detailed calculations that show how to derive the formula for c_p (equation 30) using equations 28 and 29:

$$c_p = \sum_{i=1}^{\infty} [A_i] = [A] + \sum_{i=2}^{\infty} [A_i] = [A] + \sum_{i=2}^{\infty} \sigma K^{-1}(K[A])^i$$

$$c_p = (1-\sigma)[A] + \frac{\sigma[A]}{1-K[A]}$$

Because σ and K^{-1} are both constants, they can be moved in front of the infinite series to give equation XIII.

$$c_p = [A] + \sigma K^{-1} \sum_{i=2}^{\infty} (K[A])^i \qquad \text{(XIII)}$$

The sum of the infinite series from 1 to infinity minus the first term K[A] is equal to the sum of the infinite series from 2 to infinity (equation XIV).

$$c_p = [A] + \sigma K^{-1} \left[\sum_{i=1}^{\infty} (K[A])^i - K[A] \right] \qquad \text{(XIV)}$$

The expression $\sum_{i=1}^{\infty} (K[A])^i$ is actually in the form of a Maclaurin series (equation I), so it can be solved using a method similar to how equation 27 for c_t had been solved. Substituting K[A] for z, and *i* for n, yields equation XV. The first term of the infinite series in equation XV is 1, which gives equation XVI. Subtracting 1 from both sides of equation XVI gives equation XVII, which can then be further simplified to give equation XVIII.

$$\frac{1}{1-K[A]} = \sum_{i=0}^{\infty} (K[A])^i \qquad \text{(XV)}$$

$$\frac{1}{1-K[A]} = \sum_{i=1}^{\infty} (K[A])^i + 1 \qquad \text{(XVI)}$$

$$\frac{1}{1-K[A]} - 1 = \sum_{i=1}^{\infty} (K[A])^i \qquad \text{(XVII)}$$

$$\sum_{i=1}^{\infty} (K[A])^i = \frac{1}{1-K[A]} - \frac{1-K[A]}{1-K[A]} = \frac{1-1+K[A]}{1-K[A]} = \frac{K[A]}{1-K[A]} \qquad \text{(XVIII)}$$

Substituting the expression for $\sum_{i=1}^{\infty} (K[A])^i$ given in equation XVIII into equation XIV gives equation XIX. σK^{-1} is then distributed to the terms within the bracket, and K^{-1} times K cancels to give equation XX. Combining like terms gives equation 30.

$$c_p = [A] + \sigma K^{-1} \left[\frac{K[A]}{1-K[A]} - K[A] \right] \qquad \text{(XIX)}$$

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$$c_p = [A] + \frac{\sigma[A]}{1 - K[A]} - \sigma[A] \qquad \text{(XX)}$$

Thus equation 30 is obtained: $c_p = (1-\sigma)[A] + \frac{\sigma[A]}{1-K[A]}$

Below are the detailed calculations that show how to derive the formula for the degree of polymerization in terms of number of polymers, $<dp>_n$ (equation 31). Combining equations 27 and 30 with equation 31 gives equation XXI. The terms in the numerators are given common denominators and then the numerator is multiplied by the inverse of the denominator (equations XXII and XXIII). [A]'s can cancel to give equation XXIV, and combining like terms gives equation 31.

$$< dp >_n = \frac{c_t}{c_p} = \frac{(1-\sigma)[A] + \frac{\sigma[A]}{(1-K[A])^2}}{(1-\sigma)[A] + \frac{\sigma[A]}{1-K[A]}} \qquad \text{(XXI)}$$

$$< dp >_n = \frac{\frac{(1-\sigma)[A](1-K[A])^2 + \sigma[A]}{(1-K[A])^2}}{\frac{(1-\sigma)[A](1-K[A]) + \sigma[A]}{1-K[A]}} \qquad \text{(XXII)}$$

$$< dp >_n = \frac{(1-\sigma)[A](1-K[A])^2 + \sigma[A]}{(1-K[A])^2} \times \frac{1-K[A]}{(1-\sigma)[A](1-K[A]) + \sigma[A]} \qquad \text{(XXIII)}$$

$$< dp >_n = \frac{(1-\sigma)(1-K[A])^2 + \sigma}{(1-K[A]) \times \left((1-\sigma)(1-K[A]) + \sigma\right)} \qquad \text{(XXIV)}$$

Equation 31 follows: $< dp >_n = \frac{\sigma + (1-\sigma)(1-K[A])^2}{\sigma(1-K[A]) + (1-\sigma)(1-K[A])^2}$

Below are the detailed calculations which elucidate the formula for $<dp>_w$ (equation 32). First, the Maclaurin series (equation I) can be differentiated to give equation III. Multiplying both sides of equation III by z gives the Koebe function, equation IV. Differentiating both sides of equation IV gives equation XXV. The left side of equation IV is differentiated by using the Quotient Rule. Equations XXVI to XXIX outline the algebraic steps to equation XXX. Multiplying both sides of equation XXX by z gives equation XXXI. The first term of the series is drawn to give equation XXXII. Subtracting z from both sides of equation XXXII gives equation XXXIII. Substituting z=K[A] and

n=i gives equation XXXIV. Substituting $[A_i] = \sigma K^{-1}(K[A])^i$ (equation 25) into this infinite series gives equation XXXV. Substituting the value for the infinite series (equation XXXIV) into equation XXXV gives equation XXXVI. Adding an [A] to equation XXXVI gives equation XXXVII. Equation 32 is then the ratio of equation XXXVII over equation 27. Equations XXXVIII to XLI outline the algebraic steps that lead to the formula for $\langle dp \rangle_w$ equation 32.

$$\frac{1(1-z)^2 - 2(1-z)(-1)z}{(1-z)^4} = \sum_{n=1}^{\infty} n^2 z^{n-1} \quad \text{(XXV)}$$

$$\frac{1-2z+z^2+2z(1-z)}{(1-z)^4} = \sum_{n=1}^{\infty} n^2 z^{n-1} \quad \text{(XXVI)}$$

$$\frac{1-2z+z^2+2z-2z^2}{(1-z)^4} = \sum_{n=1}^{\infty} n^2 z^{n-1} \quad \text{(XXVII)}$$

$$\frac{1-z^2}{(1-z)^4} = \sum_{n=1}^{\infty} n^2 z^{n-1} \quad \text{(XXVIII)}$$

$$\frac{(1-z)(1+z)}{(1-z)^4} = \sum_{n=1}^{\infty} n^2 z^{n-1} \quad \text{(XXIX)}$$

$$\frac{1+z}{(1-z)^3} = \sum_{n=1}^{\infty} n^2 z^{n-1} \quad \text{(XXX)}$$

$$\frac{z(1+z)}{(1-z)^3} = \sum_{n=1}^{\infty} n^2 z^{n} \quad \text{(XXXI)}$$

$$\frac{z(1+z)}{(1-z)^3} = \sum_{n=2}^{\infty} n^2 z^{n} + z \quad \text{(XXXII)}$$

$$\sum_{n=2}^{\infty} n^2 z^{n} = \frac{z(1+z)}{(1-z)^3} - z \quad \text{(XXXIII)}$$

$$\sum_{i=2}^{\infty} i^2 (K[A])^i = \frac{K[A](1+K[A])}{(1-K[A])^3} - K[A] \quad \text{(XXXIV)}$$

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$$\sum_{i=2}^{\infty} i^2[A_i] = \sum_{i=2}^{\infty} i^2 \sigma K^{-1}(K[A])^i = \sigma K^{-1} \sum_{i=2}^{\infty} i^2 (K[A])^i \qquad \text{(XXXV)}$$

$$\sum_{i=2}^{\infty} i^2[A_i] = \sigma K^{-1}\left(\frac{K[A](1+K[A])}{(1-K[A])^3} - K[A]\right) = \frac{\sigma[A](1+K[A])}{(1-K[A])^3} - \sigma[A] \qquad \text{(XXXVI)}$$

$$[A] + \sum_{i=2}^{\infty} i^2[A_i] = [A] + \frac{\sigma[A](1+K[A])}{(1-K[A])^3} - \sigma[A] = (1-\sigma)[A] + \frac{\sigma[A](1+K[A])}{(1-K[A])^3} \qquad \text{(XXXVII)}$$

$$< dp >_w = \frac{[A] + \sum_{i=2}^{\infty} i^2[A_i]}{[A] + \sum_{i=2}^{\infty} i[A_i]} = \frac{(1-\sigma)[A] + \dfrac{\sigma[A](1+K[A])}{(1-K[A])^3}}{(1-\sigma)[A] + \dfrac{\sigma[A]}{(1-K[A])^2}} \qquad \text{(XXXVIII)}$$

$$< dp >_w = \frac{(1-\sigma) + \dfrac{\sigma(1+K[A])}{(1-K[A])^3}}{(1-\sigma) + \dfrac{\sigma}{(1-K[A])^2}} \qquad \text{(XXXIX)}$$

$$< dp >_w = \frac{\dfrac{(1-\sigma)(1-K[A])^3 + \sigma(1+K[A])}{(1-K[A])^3}}{\dfrac{(1-\sigma)(1-K[A])^2 + \sigma}{(1-K[A])^2}} \qquad \text{(XL)}$$

$$< dp >_w = \frac{(1-\sigma)(1-K[A])^3 + \sigma(1+K[A])}{(1-K[A]) \times \left[(1-\sigma)(1-K[A])^2 + \sigma\right]} \qquad \text{(XLI)}$$

Hence equation 32 follows: $< dp >_w = \dfrac{\sigma(1+K[A]) + (1-\sigma)(1-K[A])^3}{\sigma(1-K[A]) + (1-\sigma)(1-K[A])^3}$