Thermodynamics of crystal nucleation in drops, hanging or sitting in an external electric field

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The influence of an external electric field on the thermodynamics and kinetics of crystal formation in spherical droplets has been studied. A numerical analysis is performed with NaCl-water system and the strength of the electric field, which would produce an appreciable change in the nucleation process, is calculated. The changes in the case of proteins and other macromolecules are discussed.

1 Introduction

Many researchers employ hanging drop and sitting drop techniques\(^1\) to crystallize proteins and other macromolecules, mainly because the sample required for the experiment is minimum. A successful crystallization experiment could be performed using only a few microlitres of protein solution. In this method, a droplet, either hanging or sitting is equilibrated against a reservoir containing a solution of the crystallizing agent at a higher concentration than the droplet. Recent reports indicate that, the presence of electric and magnetic fields would influence the nucleation of crystals in hanging and sitting drops, in many ways\(^2\). However, the findings are primitive and nobody has started dealing the situation in a quantitative fashion. This paper considers the thermodynamics of crystal nucleation in liquid drops in the presence of an externally applied electric field. The major aim of this work is to determine the optimum strength of the field that would affect the nucleation kinetics in a useful manner.

The formation of a new phase, either amorphous or crystalline, in a homogeneous, super-saturated liquid or vapor phase is considered as the result of thermodynamic fluctuations taking place in the system\(^3\). The creation of the free surface of the new phase is energetically unfavourable and the cluster formed does not transform into a macroscopic crystal, unless it reaches a critical size\(^4\). The isothermal and isobaric free energy required for the formation of cluster of a new phase out of g molecules, in the presence of an electric field is given by:\(^5\)

\[
\Delta G = \Delta G_{\text{sp}} + \Delta G_{\text{pr}} + \Delta G_{\text{el}} \quad \ldots(1)
\]

The surface term, \(\Delta G_{\text{sp}}\), is always positive and the volume term is negative as far as the concentration \(C\) of the initial supersaturated phase is greater than the equilibrium concentration \(C^\text{eq}\). The third term is the contribution of the electric field to the total energy of formation of the cluster. Assuming that the cluster formed is a sphere of radius \(r\) and employing the results of the classical nucleation theory\(^6\), the first two terms are expanded to yield:

\[
\Delta G = 4\pi r^3 \sigma - g kT \ln \left( \frac{\gamma}{\gamma^\text{eq}} \right) + \Delta G_{\text{el}} \quad \ldots(2)
\]

where \(\sigma\) is the interfacial tension, \(\gamma\) and \(\gamma^\text{eq}\) are the activity coefficients of the super-saturated state and equilibrium state respectively of the solution. Some workers\(^7\) have reported the value of \(\Delta G_{\text{el}}\), but none of them considered the curvature of the mother face which has a crucial role to play in the present case. For the hanging and sitting drops, it is reasonable to assume that, the mother phase is spherical in shape. In brief, the geometry of the present problem is a few spherical crystalline clusters nucleating in a spherical liquid droplet placed in an electric field created between two parallel metallic plates. Let \(E\) be the external electric field, \(E_{\text{u}}\) the uniform electric field in the liquid droplet and \(E_{\text{e}}\) the electric field in a spherical crystalline cluster.
Following the method of Griffiths\(^\text{10}\) we write:

\[ E_a = 3E/(2 + K_a) \quad \text{(3)} \]

and

\[ E_c = 3E_a/(2 + K_c) \quad \text{(4)} \]

where \(\varepsilon_0\) represents the permittivity of free space. Making use of Eqs (3) and (4) and performing the integration, the above equation becomes:

\[ \Delta G_{\text{fe}} = -9\varepsilon_0 g \omega E^2[K_a - (9K_c/(2 + K_c)^3)]/2(2 + K_a)^2 \quad \text{(7)} \]

In this equation, \(\omega\) stands for the volume of a single kinetic element. Combining Eqs (2) and (7) results in:

\[ \Delta G = 4\pi \sigma r^2 - gkT \ln (\gamma C/\gamma^*C^*) \\
- 9\varepsilon_0 g \omega E^2[K_a - (9K_c/(2 + K_c)^3)]/2(2 + K_a)^2 \]

Neglecting the small variation of \(\gamma\) with concentration and introducing a constant:

\[ \Psi = 9\varepsilon_0 \omega [K_a - (9K_c/(2 + K_c)^3)]/2kT (2 + K_a)^2 \quad \text{(8)} \]

the above equation is read as:

\[ \Delta G = 4\pi r^2 \sigma - gkT (\ln \beta + \Psi) \quad \text{(9)} \]

where \(\beta = C/C^*\) is the initial super-saturation ratio.

Eqs (8) and (9) reveal that, for a system with \(K_a > 9K_c/(2 + K_c)^2\), \(\Psi\) becomes a positive quantity and the effect of electric field results in a decrease of the free energy of formation and consequent increase in

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**Fig. 1** — Percentage increase in the concentration of nuclei as a function of the applied electric field, for different supersaturation ratios. (B = 1.005; C = 1.00625; D = 1.0075)

Here, \(K_a\) and \(K_c\) are the dielectric constants of the liquid phase and crystalline phase respectively. Substituting for \(E_m\), Eq. (4) takes the form:

\[ E_c = [3/(2 + K_c)] [3/(2 + K_a)] E \quad \text{(5)} \]

Now, the electric contribution to the work of cluster formation could be expanded as:\(^\text{11}\):

\[ \Delta G_{\text{fe}} = \Delta (1/2 \int D.E \, d\Omega) \]

\[ = 1/2 \int (D_cE_c - D_aE_a) \, d\Omega \]

Here, the integration is performed over the volume \(\Omega\) of \(g\) molecules; \(D_c\) and \(D_a\) represent the electric displacement vectors in the crystalline and amorphous phases respectively. Treating the initial and final phases as linear dielectrics, the above equation yields:

\[ \Delta G_{\text{fe}} = 1/2 \int (\varepsilon_0 K_aE_c^2 - \varepsilon_0 K_aE_a^2) \, d\Omega \quad \text{(6)} \]
nucleation rate. On the other hand, if \( K_a < 9 K_c / (2 + K_c)^2 \), an inhibition in nucleation rate is expected. Making use of the equation \( 4 \pi r^3/3 = g \theta \) and minimizing \( \Delta G \) with respect to \( r \), one finds the radius of the critical nucleus as:

\[
r^* = 2 \sigma \omega / kT (\ln \beta + \Psi E^2)
\]

...(10)

The value of the critical free energy determined is:

\[
\Delta G^* = 16 \pi \sigma \omega / 3 kT (\ln \beta + \Psi E^2)^2
\]

...(11)

The corresponding equations for \( r^* \) and \( \Delta G^* \) obtained in the absence of electric field do not contain the second term of the denominator. Thus, the electric field decreases the critical radius and critical free energy of formation for all positive values of \( \Psi \) and vice versa. The concentration of critical nuclei formed in the mother phase within a given time could be calculated by employing the classical nucleation theory \(^{12} \) to yield:

\[
N^* = N_j \exp(-\Delta G^*/kT)
\]

...(12)

where \( N_j \) is the concentration of monomers. Combining Eqs (11) and (12), this becomes:

\[
N^* = N_j \exp(-[16 \pi \sigma \omega / 3 kT \ln \beta + \Psi E^2])
\]

...(13)

Elimination of the second term in the denominator of the exponential results in the equation for the concentration of nuclei in the absence of electric field.

\[
N^* = N_j \exp(-[16 \pi \sigma \omega / 3 kT \ln \beta])
\]

...(14)

Let us examine the extent of the electric field influence on a simple model system, namely, sodium chloride nucleating in aqueous medium at 300 K. For this system\(^{19} \), \( K_c = 5.62, K_a = 80, \omega = 4.85 \times 10^{-9} \text{m}^3 \text{F}^{-1} \text{m}^{-1} \text{m}^2 \) and hence, the value of \( \Psi \) is \( 0.54 \times 10^{-9} \). In practice, we can set the maximum value of \( E \) at \( 10^6 \text{V/m} \), since the application of a higher field may result in the dielectric breakdown of air and the other samples involved. This immediately indicates that, \( \Psi E^2 \) is very small compared to \( \ln \beta \) for all values of practical interest of \( E \) and \( \beta \).

Dividing Eq. (13) by Eq. (14) and neglecting the higher powers of \( \Psi E^2 \), one finds the ratio of the concentrations of the critical nuclei, with and without the field as:

\[
N^*/N_j^* = \exp(\xi \Psi E^2 (\ln \beta + \Psi E^2)^2)
\]

...(15)

where, \( \xi = 32 \pi \sigma \omega / 3 kT^3 \).

Neglecting \( \Psi E^2 \) compared to \( \ln \beta \), this equation takes the form:

\[
N^*/N_j^* = \exp(\xi \Psi E^2 (\ln \beta)^2)
\]

...(16)

Substituting \( \sigma = 10^4 \text{J/m}^2 \), we find that \( \xi = 1.11121 \times 10^3 \text{S.I. units} \). Table 1 lists the percentage variation in critical nuclei concentration as a function of the applied electric field, for different super-saturation levels. It indicates that, for the super-saturation levels 1.005 to 1.01 electric fields slightly greater than \( 10^4 \text{V/m} \) would influence the concentration of critical nuclei. For super-saturation ranging from 1.01 to 1.05, fields greater than \( 10^4 \text{V/m} \) are required to create any appreciable change in nucleation. The percentage variations in the concentration of the critical nuclei as a function of the applied electric field are depicted in Figs 1 and 2, for the two super-saturation regions, mentioned above. For proteins and other
macromolecules, the size $\omega$ of a molecule is very large compared to that of small molecules. Realizing the fact that, the exponent in Eq. (16) is proportional to the third power of $\omega$ through $\xi$ and $\Psi$, it is envisaged that, electric fields of strength even less than $10^4$ V/m would affect the nucleation of macromolecules in hanging and sitting drops.

It has become evident that, in any crystal growth experiment using hanging and sitting drops, an externally applied electric field may promote or inhibit nucleation, depending on the value of a parameter $\Psi$ defined in this discussion. Furthermore, the influence due to a given electric field will be stronger on large molecules. The proposed theory and the numerical analysis show that, electric fields of strength $10^4$ to $10^6$ V/m are required to affect the nucleation process of small molecule crystals. Proteins and other macromolecules have larger monomer size and hence electric fields weaker than even $10^4$ V/m may influence their nucleation.

References