

A model for swelling changes in a covalently crosslinked gel caused by unfolding of folded domains

Karel Dušek¹, Miroslava Dušková-Smrčková¹, Russell Stewart², Jindřich Kopeček³

¹ Institute of Macromolecular Chemistry, Academy of Sciences of the Czech Republic, 162 06 Prague 6, Czech Republic

² Department of Bioengineering, University of Utah, Salt Lake City, UT 84112, USA

³ Department of Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT 84112, USA

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Abstract

A model describing swelling changes of covalently crosslinked gels caused by unfolding of crosslinks of folded chains built-in in the gel matrix was proposed. By unfolding, a new interacting surface is exposed which may differ from the interacting sites of the gel polymer. Non-ionic as well as ionic interactions are considered. A certain force generated by the swelling pressure acts on the ends of the folded crosslinks and unfolding starts when this force exceeds a certain limiting value. The continuation or arrest of unfolding depends on whether the exposure of the new interacting surface decreases or increases this force. The unfolding process is considered to be irreversible but possible reversibility can be considered. This model relates to biohybrid gels in which the folded domain of the crosslink is composed of elements of the muscle protein titin. The model is based on the statistical-mechanical theory of swelling of crosslinked polymers. A change in external variables such as temperature or degree of ionization can cause an abrupt change in volume of the swollen gel (transition) within a certain range of parameters characterizing the gel and polymer-solvent interactions.

Introduction

The swelling degree of a covalently crosslinked polymer is determined by several factors, such as polymer-solvent interactions, crosslinking density, conditions at network formation and, in the case of polyelectrolytic systems, degree of ionization, and presence of external electrolyte. The equilibrium degree of swelling can also be affected by possibly existing physical crosslinks, such as crystallites, or strongly associated structures. Externally, the degree of swelling is controlled by temperature, solvents nature and composition, addition of non-ionizable and ionizable compounds, etc.

A certain balance of attractive and repulsive interactions may lead to a special kind of compensation, such that two network phases of different degrees of swelling can coexist in equilibrium. The transition between the two states of the network is called *volume phase transition* or *collapse transition* (1,2).

The continuous or transition swelling changes caused by dissociation and reformation of physical domains acting as crosslinks are characteristic of several polymer-solvent systems, mainly of biopolymer gels (3-5). By dissociation of associated (folded) domains a new interacting surface is exposed which usually leads to an increase in equilibrium swelling, but sometimes a hydrophobic interacting surface is exposed like in the case of coiled-coil domains (5).

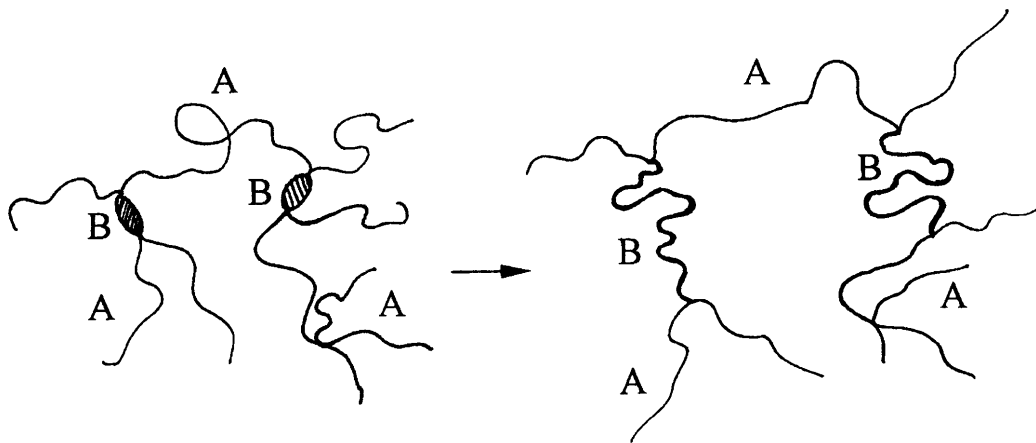
Some of the elements consisting of folded chains unfold when a certain limiting stress is applied to the chain ends. A muscle protein titin is a single-chain giant molecule of molecular weight about 3 million composed of 27,000 amino acids. A titin molecule contains more than 200 immunoglobulin (Ig) and fibronectin domains. A repeating Ig domain representing a folded element is a sandwich of two antiparallel β -sheets held together by hydrophobic interactions between the β -sheets in the core of the domain and by hydrogen bonds between the β -strands. When individual titin molecule is stretched, the Ig domains unfold one after another. Using atomic force microscope or optical tweezer, a periodic (sawlike) force-distance record was obtained corresponding to successive unfolding of Ig domains (6). Models based on thermodynamic and dynamics simulation describing the unfolding behavior of titin molecules were devised (7-9).

Chen, Kopecek, and Stewart designed a hydrophilic (polyacrylamide) gel crosslinked with Ig domains (4). The external force applied to the folded chain ends through the AFM tip in an AFM experiment was replaced by the osmotic pressure produced by swelling of a hydrophilic network. It was expected that unfolding of Ig domains as a result of changing osmotic pressure would lead to an increase in the degree of swelling. The first experiments have shown that a change in temperature produced a large change in the degree of swelling associated with Ig denaturation. The unfolding was not reversible.

In this contribution, a simple thermodynamic model is proposed for swelling changes of a network crosslinked by folded domains which unfold irreversibly after a limiting osmotic force acting on crosslink domain ends is reached. It will be shown that the swelling changes can be continuous or discontinuous. This model reflects some features of swelling changes of the poly(acrylamide) gels with immunoglobulin crosslinks (4) but would require further tuning before it is applied to this particular system.

Swelling Changes

The model: The model of the network under consideration and its swelling transition is shown below:



The chains A are network chains; by their solvation (hydration), swelling pressure is generated. B are folded domains with a small interacting surface acting as tetrafunctional crosslinks. The swelling pressure is counterbalanced by the elastic force arising from stretching chains A. Above a limiting force, the crosslinks unfold one after an-

other and the inner surface of the folds is exposed for interaction with the solvent. Moreover, the unfolded chains start contributing to elastically active network chains (EANC) and one tetrafunctional crosslink is transformed into two trifunctional ones. The interacting surface of the unfolded chain B is allowed to be different compared with the surface of chain A. In this contribution, the elasticity behavior of network chains is considered to be Gaussian in the present version, but introduction of the finite extensibility condition is possible.

The Gibbs energy change on swelling of a gel with ionizable groups is considered to be composed of the following contributions (10,11)

$$\Delta G_{sw} = \Delta G_{mix} + \Delta G_{def} + \Delta G_{elst} + \Delta G_{ion} \quad (1)$$

The terms ΔG_{sw} , ΔG_{mix} , ΔG_{def} , ΔG_{elst} , and ΔG_{ion} refer, respectively, to swelling, mixing of polymer segments with solvent molecules, deformation of the network, electrostatic repulsion due to fixed charges, and the effect of small ions (Donnan effect).

The equilibrium swelling degree given by the volume fraction of the polymer in the swollen network, ϕ_2 is obtained by solution of the equation

$$\Pi_{sw} = - \left(\frac{1}{V_1} \right) \left(\frac{\partial \Delta G_{sw}}{\partial N_1} \right)_{T,p,N_2} = - \frac{1}{V_1} \Delta \mu_1 = - \frac{RT}{V_1} \ln a_1 = 0 \quad (2)$$

where Π_{sw} is the swelling pressure and V_1 , N_1 , $\Delta \mu_1$, and a_1 are, respectively, molar volume of the solvent, number of moles of the solvent, change of the chemical potential of the solvent, and solvent activity. If the contributions to ΔG_{sw} are differentiated with respect to N_1 , the following contributions to Π_{sw} can be derived

$$\Pi_{sw} = \Pi_{mix} + \Pi_{def} + \Pi_{ion} + \Pi_{elst} \quad (3)$$

The model is based on the Flory-Huggins theory of polymer solution, Flory-Erman (F-E) theory of rubber elasticity, and extended Katchalsky-Lifson model of ionic gels. For the manifestation of the phenomenon, here we limit ourselves to the elasticity of *Gaussian* chains but the extension to non-Gaussian behavior is straightforward. The contributions to Π_{sw} are as follows:

$$\Pi_{mix} = -(RT/V_1) [\ln(1 - \phi_2) + \phi_2 + \chi(\phi_2)\phi_2^2] \quad (4)$$

$$\Pi_{def} = -RT\nu_d(A_f\phi_0^{2/3}\phi_2^{1/3} - B\phi_2) \quad (5)$$

$$\Pi_{ion} = (RT/M_0) \left(i\rho\phi_2 - 2f_{-c-}M_0 \left[\left(1 + \frac{i\rho\phi_2}{M_0f_{-c-}} \right)^{1/2} - 1 \right] \right) \quad (6)$$

$$\Pi_{elst} = RT \frac{\nu_d N_A Z i^2 e^2 \phi_2^{4/3}}{3D(\bar{r}_0^2 \phi_0^{-2/3})^{1/2}} \left(\frac{2.5A}{1+A} - \ln(1+A) \right) \quad (7)$$

where

$$A = 6r/\kappa\bar{r}_0^2 = \left(\frac{\phi_0^{2/3}\phi_2^{-2/3}DkTM_0}{\pi N_A e^2 \bar{r}_0^2 (2M_0c_- + i\rho\phi_2)} \right)^{1/2}$$

In these equations, ν_d is the concentration of elastically active network chains (EANC) in unit dry volume, $\chi(\phi_2)$ is polymer-solvent interaction parameter which may depend

on ϕ_2, A_f is the front factor varying from $(f_c - 2) / f_c$ to 1 in the F-E junction fluctuation theory; the factor B varies from 0 to $2 / f_c$, where f_c is the average number of strands with infinite continuation per elastically active crosslink, M_0 is molecular weight of the monomer, i is the degree of ionization of the polymer (fraction of charged groups), ρ is density of the dry polymer, c_- is concentration of coions (small anions, if the polymer is negatively charged, f^- is activity coefficient of coions, r is end-to-end distance of a network chain in the swollen state \bar{r}_0^2 is mean-squared end-to-end distance of a network chain in the unperturbed state, D is permittivity of the medium, N_A is Avogadro number, and Z is degree of polymerization, e is unit charge, κ is inverse of the Debye radius of the ion atmosphere.

It is legitimate to use volume fractions in the mixing term if the interacting elements (base units) have approximately the same interacting surface/volume ratios, r_s . However, in the case discussed here for the folded domain, r_s is much smaller than for the unfolded structure, and surface fractions ψ_2 should be used instead of the volume fractions ϕ_2 . This idea was already put forward by Tompa (12).

Limiting force to unfold folded crosslink

The contribution by the deformation of the network, ΔG_{def} , is composed of the contribution by chain stretching (elasticity) and other entropic changes associated with deformation-dependent interactions between network chains,

For Gaussian chains and isotropic three-dimensional deformation (swelling) (13,14)

$$\Delta G_{\text{def}} = 3kTAn_e \left(\left(\frac{V}{V_0} \right)^{\frac{2}{3}} - 1 \right) + kTBn_e \ln \left(\frac{V}{V_0} \right) \quad (8)$$

where V and V_0 are the volumes of the isotropic swollen network and network in the reference state, respectively; n_e is the number of elastically active network chains which is a function of the number of elastically active crosslinks.

The reference state is important for the considerations below. It is defined as a state at which, on average, the chains are at a state of normal coiling (state of ease) and, therefore, their ends do not exert any force on crosslinks (13). It is assumed, as a first approximation, that such situation is met at network formation if the medium is such that the uncrosslinked chains would assume unperturbed conformations. In the absence of excluded volume effect, the ratio of the end-to-end distance of the network chains in the dry state to that in the reference state, $(\bar{r}_d^2)/(\bar{r}_0^2)$ is related to the volume fraction of polymer at network formation (1,2,13)

$$\phi_0 = \left(\frac{\bar{r}_d^2}{\bar{r}_0^2} \right)^{3/2}$$

The force produced by the four stretched elastically active chains A acting on the crosslink B (Fig. 1), f^* , is related to the swelling pressure contribution Π_{def} per crosslink. The retractive force is derived from Eqs. (1-3) and is considered relative to the reference state at which, by definition, no forces act on a crosslink (state $\phi_2 = \phi_0$).

$$f^* = \left(\frac{\Pi_{\text{def}}}{n_e} - \frac{\Pi_{\text{def}(0)}}{n_e} \right) \quad (9)$$

For Π_{def}

$$\Pi_{\text{def}} = kT[A_f n_e V^{-1/3} V_0^{-2/3} + B n_e (1/V)] \quad (10)$$

The force per EANC reads

$$f^* = \frac{\Pi_{\text{def}} V_{2/3}}{n_e} = \frac{kT}{V_{\text{molec}}^{1/3}} [A_f (\phi_0^{2/3} \phi_2^{-1/3} - \phi_0) - B \phi_2] \quad (11)$$

where V_{molec} is the molecular volume of a non-swollen EANC. The force per chain, relative to the reference state characterized by ϕ_0 , then reads

$$f_{\text{rel}}^* = 2 \frac{kT}{V_{\text{molec}}^{1/3}} [A_f (\phi_2^{-1/3} \phi_0^{2/3} - B(\phi_2 - \phi_0))] \quad (12)$$

There exists a critical force, $f_{\text{rel,crit}}^*$, necessary to unfold the crosslink

$$f_{\text{rel}}^* \geq f_{\text{rel,crit}}^* \quad (13)$$

Swelling Changes due to Unfolding

Unfolding of the crosslinks causes changes in the magnitude and character of the interacting surface, concentration of EANC's, and possibly fraction of ionizable groups. Therefore, several parameters of the swelling equation become a function of the unfolding parameter. For the purpose of demonstration of the unfolding effect, the system will be simplified by neglecting the effect of electrostatic repulsion and only the Donnan effect will represent the effect of charges.

In a network with crosslinks in folded state, a part of segments is buried inside the domain and is excluded from contact with the solvent. The mixing term is determined by the interacting surface. Therefore, the volume fraction, ϕ_2 , is replaced by the surface fraction ψ_2 defined by

$$\psi_2 = \frac{x_f b (w_f / \rho_f) + (1 - x_f) w_f / \rho_f + w_{\text{pg}} / \rho_{\text{pg}}}{x_f b (w_f / \rho_f) + (1 - x_f) w_f / \rho_f + w_{\text{pg}} / \rho_{\text{pg}} + w_s / \rho_s} \quad (14)$$

where w_f , w_{pg} , and w_s are weight fractions of folding domains, gel polymer, and solvent, respectively. ρ_f , ρ_{pg} , and ρ_s are the respective densities, and x_f is the fraction of the folding polymer in the folded state.

The factor b characterized the fraction of the total interacting surface (available after unfolding) in the folded state. The value of the b is estimated to be of the order of 10^{-1} .

The mixing contribution before unfolding is thus replaced by

$$\Pi_{\text{mix}} = -(RT/V_1) [\ln(1 - \psi_2) + \psi_2 + \bar{\chi}(\psi_2) \psi_2^2] \quad (15)$$

where $\bar{\chi}$ is contributed by the fractions of the respective surfaces

$$\bar{\chi} = \psi_g \chi_g + \psi_f \chi_f + \psi_u \chi_u \quad (16)$$

ψ_g , ψ_f , and ψ_u are surface fractions of the gel polymer, folded domain, and unfolded domain, respectively, and χ_g , χ_f , and χ_u , the respective contributions to the interaction parameter.

Also, the concentration of EANC's changes because upon unfolding; one tetrafunctional folded crosslink is transformed into two trifunctional ones. The total concentration of EANC's ν_d is the sum of the contributions of conventional crosslinks possibly existing in the gel polymer $(\Delta\nu_d)_{pg}$ and folding crosslinks $(\Delta\nu_d)_f$

$$\bar{\nu}_d = (\Delta\nu_d)_{pg} + (\Delta\nu_d)_f[x_f + (3/2)(1 - x_f)] \quad (17)$$

Similarly, the functionality of an elastically active crosslink is given by

$$f_e = (\Delta f_e)_{pg} + (\Delta f_e)_f \frac{4x_f + 6(1 - x_f)}{x_f + 2(1 - x_f)} \quad (18)$$

The magnitude of the contributions depends on the particular gel structure (topological defects, etc.) The molecular volume of an EANC appearing in Eq. (11) is given by the relation

$$V_{molec} = \frac{1}{\bar{\nu}_d N_A} \quad (19)$$

The crosslink domain upon unfolding can contribute by a certain number of ionized groups. Assuming that neither the network chains of the gel polymers nor the surface of the folded domain bear charged groups,

$$\Pi_{ion} = (RT/M_0)[i\rho_f\phi_2(1 - x_f)] \quad (20)$$

where here M_0/i is equal to the equivalent weight of both network polymer and folded domain per fixed charge and one has to consider the possible "dilution" by the gel polymer. Therefore, the swelling equilibrium is determined by the following equation, used for demonstration of the swelling transition

$$-\ln(1 - \psi_2) + \psi_2 + \bar{\chi}(\psi_2)\psi_2^2 - \bar{\nu}_d(A_f\phi_0^{2/3}\phi_2^{1/3} - B\phi_2) + (1/M_0)(i\rho_f\phi_2(1 - x_f)) = 0 \quad (21)$$

The swelling behavior can be changed by variation of external parameters, like temperature, and, in the case of polyelectrolyte networks, degree of ionization and ionic strength. The changes in temperature or solvent composition are reflected in changes of $\bar{\chi}$. Initially, the force acting on crosslinks is lower than the critical force ($(f_{rel}^* < f_{rel,crit}^*)$, $x_f = 1$ and the swelling degree increases as a result of a decrease in $\bar{\chi}$. When f_{rel}^* reaches $f_{rel,crit}^*$, the effect of variation of x_f on f_{rel}^* , while keeping the values of all other parameters constant, is examined. If $(f_{rel}^* - f_{rel,crit}^*) > 0$, unfolding of crosslinks will promote further swelling and the increase in swelling will continue until a fully unfolded state is reached ($x_f = 0$). The swelling degree changes abruptly, i.e., the transition is discontinuous. Alternatively, if the difference $(f_{rel}^* - f_{rel,crit}^*)$ becomes negative again at a certain value of x_f , the unfolding process is stopped. Then, further increase in the swelling degree proceeds by lowering of $\bar{\chi}$ by keeping x_f constant. The discontinuity region is narrower than in the previous case. If the condition $(f_{rel}^* - f_{rel,crit}^*) > 0$ is never met at all values of $\bar{\chi}$, the swelling degree is controlled by $x_f = 1$ and the swelling curve is continuous. Also, hypothetically, the swelling curve would be continuous at any value of $\bar{\chi}$ if $(f_{rel}^* - f_{rel,crit}^*) > 0$, then $x_f = 0$.

A few examples in Fig. 2 illustrate this behavior when $\bar{\chi}$ decreases. The appearance of a discontinuous transition (abrupt increase in the degree of swelling) exists in a certain range of crosslinking densities. In all these cases, the fraction of folded domains x_f

changed from 1 to 0 in one step. It is interesting to note that the χ -values of the transition pass through a maximum, the maximum value being mainly dependent on ϕ_0 . The crossover point at high values of χ and ϕ_2 is determined by the condition

$$A_f \phi_0^{2/3} \phi_2^{1/3} - B \phi_2 = 0 \quad (22)$$

At this point, the crosslinking degree does not affect swelling at all. At even higher values of χ , the network chains are much more compressed with respect to the reference state and, as a result, the swelling degree increases with increasing crosslinking density.

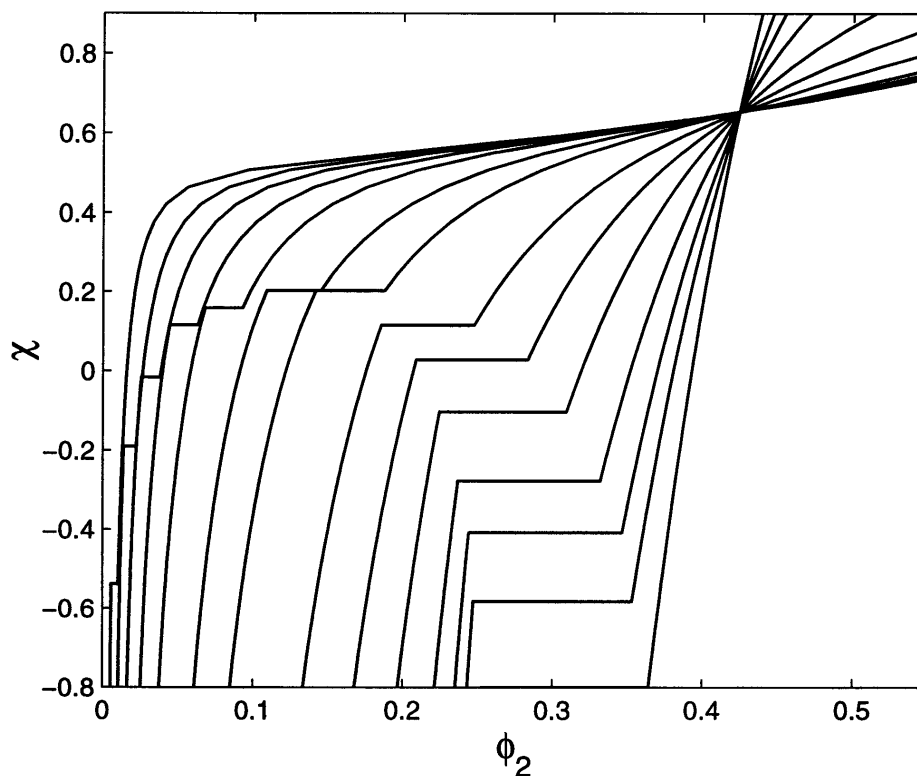


Figure 2

Calculated change of the volume fraction of the polymer in the swollen network for gels of different crosslinking densities. Decreasing χ

Examples calculated for $A_f = 1$, $B = 1$, $T = 298$, $\phi_0 = 0.15$, $b = 0.1$, $M_0/i = 200$, $\rho_f = \rho_{pg} = 1.2$, $\rho_s = 1.0$, $V_1 = 50$ ml/mol, $w_{pg}/w_f = 2|f_{rel,crit}^* = 2.13 \times 10^{-13}$ N;

The concentration of EANC's, \bar{v}_d , in mol/ml varies from left to right (at $\chi = 0$): 2×10^{-5} , 5×10^{-5} , 1×10^{-4} , 2×10^{-4} , 4×10^{-5} , 1×10^{-3} , 2×10^{-3} , 6×10^{-3} , 1.2×10^{-2} , 2.2×10^{-2} , 4×10^{-2} , 6×10^{-2} , 8×10^{-2} , 1.2×10^{-1} .

Because the transition is considered to be irreversible, increasing χ after uncoiling causes deswelling along another line, since x_r remains equal to zero (Fig. 3).

This example shows that, under certain conditions, gels containing folded domains can undergo a discontinuous swelling transition.

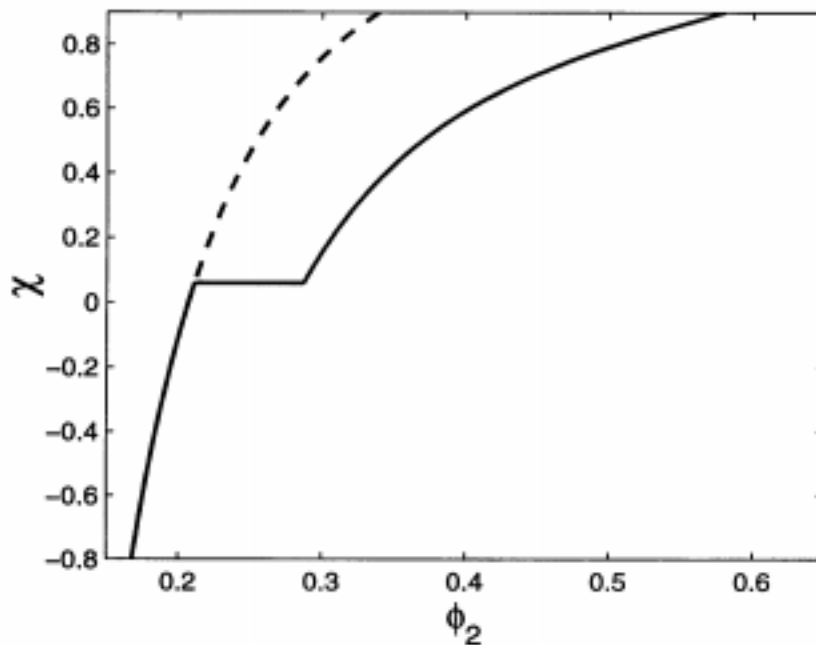


Figure 3

Calculated change of the volume fraction of the polymer in the swollen network.
 Decreasing and increasing χ .
 $\bar{\nu}_d = 1.2 \times 10^{-2}$ mol/ml; continuous line: decreasing χ , dashed line: increasing χ

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