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Authors

Coen, C.J.
Newman, J.
Blanch, H.W.
et al.

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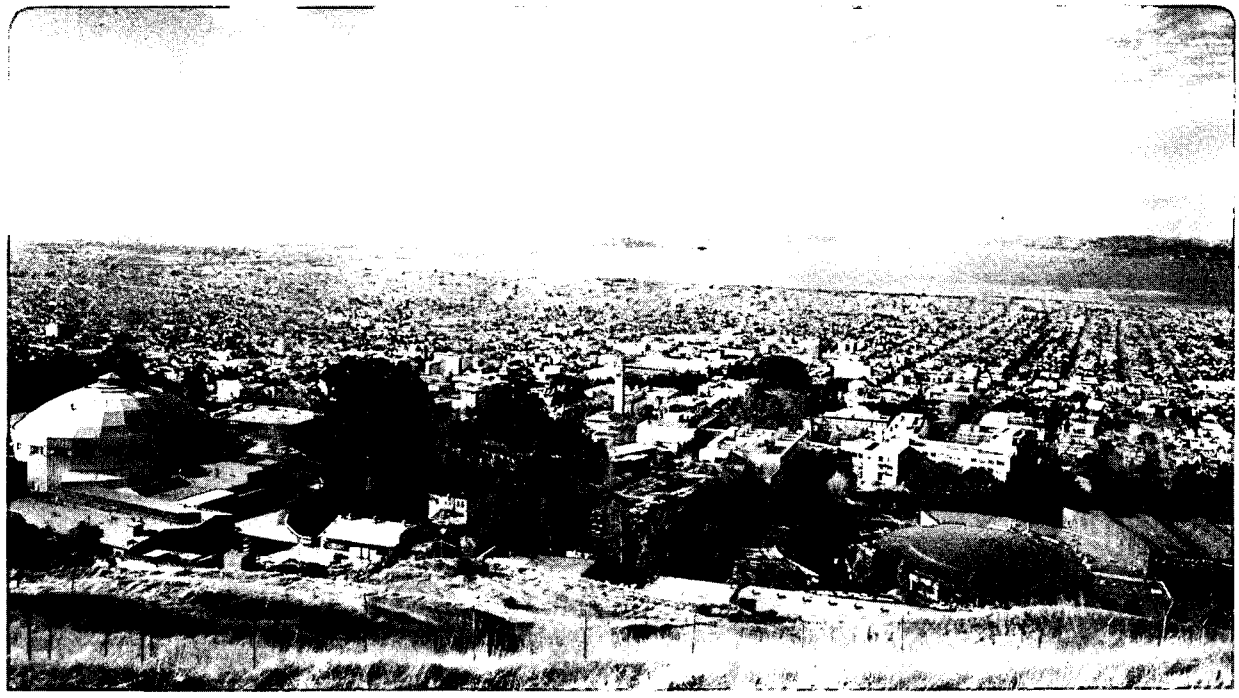

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Electrostatic Protein-Protein Interactions: Comparison of Point-Dipole and Finite-Length Dipole Potentials of Mean Force

Christopher J. Coen, John Newman, Harvey W. Blanch, and John M. Prausnitz

Department of Chemical Engineering
University of California, Berkeley

and

Chemical Sciences Division
Lawrence Berkeley Laboratory
University of California
Berkeley, California 94720

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Abstract

Based on summation of coulombic interactions, a model is developed for finite-length dipole potentials of mean force. Point-dipole and finite-length dipole potentials of mean force are compared for protein-protein interactions using parameters for bovine α-chymotrypsin. The two approximations made in the commonly-used analytical point-dipole potentials of mean force are not valid at distances near contact. Relative to the finite-length dipole model, the high-temperature approximation overpredicts, and the point-dipole approximation underpredicts charge-dipole and dipole-dipole attractions.

I. Introduction

Modeling electrostatic interactions of aqueous proteins with other proteins, charged species or surfaces is important for applications such as protein precipitation, chromatography and aqueous two-phase separations. In current models for protein-protein electrostatic interactions, the proteins are typically considered to be uniformly charged spheres; however, this description is unsatisfactory at small separation distances where the specific charge distribution of the protein is significant. Inclusion of the dipole moment provides a first level of refinement. Point-dipole interactions have been used to model protein-protein electrostatic pair potentials (1-3); however, these point-dipole expressions are inadequate at protein center-to-center separation distances less than 2 or 3 protein diameters (4, 5).

Phillies (6) described electrostatic interactions between two spherical polyelectrolytes based on representation of the charge distribution by spherical harmonics. Analytical forms for monopole and point-dipole interactions were presented. The linearized Poisson-Boltzmann equation has been numerically solved to obtain the electrostatic potential about an asymmetrically charged polyion (7-9); from that electrostatic potential, the pair potential between two polyions may be calculated. Recently, Roush et al. (9) numerically solved the linearized Poisson-Boltzmann equation for the electrostatic interaction of rat cytochrome b_5 with a charged surface and observed an orientation-dependent potential energy. As an alternative to solving the linearized Poisson-Boltzmann equation numerically, approximating protein charge distributions as dipoles may provide an adequate representation of electrostatics (3).

In this paper, we employ a finite-length dipole model as a simple, approximate method for including protein-charge distribution effects in models for the potential of mean force. Protein-protein electrostatic pair potentials are modeled using finite-length dipole interactions based on summation of coulombic interactions. Expressions for the angle-averaged charge-dipole and dipole-dipole pair potentials for the finite-length case are compared to those for the zero-length

case (ideal dipole interaction). Illustrative calculations are given for aqueous bovine α-chymotrypsin.

II. Electrostatic Model

Point Dipoles

For point dipoles, the electrostatic work required to bring two molecules from an infinite separation distance to a distance r is given by Eqs. [1] and [2] for the charge-dipole ($w_{q\mu}$) and dipole-dipole ($w_{\mu\mu}$) interactions, respectively (4, 5)[1].

$$w_{q\mu}(r,\theta_2) = -\frac{q_1\mu_2}{\varepsilon r^2}(\cos\theta_2) \qquad [1]$$

$$w_{\mu\mu}(r, \theta_1, \theta_2, \phi_{21}) = -\frac{\mu_1\mu_2}{\varepsilon r^3}(2\cos\theta_1\cos\theta_2 - \sin\theta_1\sin\theta_2\cos\phi_{21}) \qquad [2]$$

where q is the net charge, μ is the dipole moment, and $\varepsilon = 4\pi\varepsilon_0\varepsilon_r$ where ε_0 is the vacuum permittivity and ε_r is the relative permittivity or dielectric constant. Angles are defined in Figure 1 and are the same as those for the finite-length dipole case. For dipole-dipole interactions, the angles ϕ_1 and ϕ_2 yield only one independent angle: $\phi_{21} = \phi_2 - \phi_1$. For the charge-dipole interaction, a point charge placed at the origin of the dipole 1 coordinate system replaces dipole 1.

To obtain an angle-averaged potential of mean force, $\overline{w}_{ij}(r)$, for these dipole interactions, the angle-dependent potential of mean force, $w_{ij}(r, \theta_1, \theta_2, \phi_{21})$, is averaged over all configurations. The angle-averaged potential of mean force is given by the free-energy average (5)

[1] Eqs. [1] and [2] describe potentials of mean force, since the presence of the solvent is, through the dielectric constant, effectively averaged over all orientations.

$$\overline{w}_{ij}(r) = -kT \ln\left(\frac{\int \exp\left(\frac{-w_{ij}(r, \theta_1, \theta_2, \phi_{21})}{kT}\right) d\Omega}{\int d\Omega}\right) \qquad [3]$$

$$d\Omega = \sin\theta_1 \sin\theta_2 \, d\theta_1 \, d\theta_2 \, d\phi_{21}$$

where k is Boltzmann's constant and T is the absolute temperature.

Approximate analytical solutions of Eq. [3] can be obtained for the charge-dipole and dipole-dipole expressions in Eqs. [1] and [2] by expanding the exponential in [3] and truncating after the quadratic terms. The resulting expressions (5) are given by

$$\overline{w}_{q\mu}(r) = -\frac{1}{6}\frac{q_1^2\mu_2^2}{\varepsilon^2 r^4 kT} \qquad [4]$$

$$\overline{w}_{\mu\mu}(r) = -\frac{1}{3}\frac{\mu_1^2\mu_2^2}{\varepsilon^2 r^6 kT}. \qquad [5]$$

Truncation of the series requires that $w_{ij} < kT$ (the high-temperature approximation), which may not hold for proteins with dipole moments on the order of hundreds of Debye.

Finite-Length Dipoles

The finite-length dipole model considers dipoles as pairs of point charges ($\pm q'$) separated by distance L. Figure 1 defines the geometry for the finite-length dipole interactions. For the charge-dipole interaction, a point charge replaces dipole 1. By summing the individual coulombic interactions, the electrostatic work of bringing a dipole from infinity to a separation distance r (the pair potential) is calculated as a function of r, θ_1, θ_2 and ϕ_{21}. The self energies (i.e., the intra-dipole coulombic interactions) are not important here as we desire the pair potential. Thus, only molecule 1-molecule 2 terms are considered. The pair potential resulting from the sum of coulombic potential energies is

$$w_{12}\left(r, \theta_1, \theta_2, \phi_{21}\right) = \frac{1}{2\varepsilon}\sum_{l=1}^{n_1}\sum_{m=1}^{n_2}\frac{q_l' q_m'}{r_{lm}\left(r, L, \theta_1, \theta_2, \phi_{21}\right)} \qquad [6]$$

where n_1 is the total number of charges on molecule 1 and n_2 has a similar definition; l and m are indices for the charges of molecules 1 and 2, respectively; and r_{lm} is the distance between each pair of charges. The finite-length dipole potentials of mean force are then calculated by substituting Eq. [6] into Eq. [3] and integrating numerically. These calculations relax both the point-dipole and high-temperature approximations.

III. Results

Point Dipoles

Figures 2(a) and (b) show comparisons between the approximate, analytical point-dipole expressions (Eqs. [4] and [5]) and the numerical integration of the angle-dependent point-dipole expressions (Eqs. [1] and [2]). The numerical integration relaxes the high-temperature approximation made in Eqs. [4] and [5]. The dipole moment (2), net charge (2) and dielectric constant are those of aqueous α-chymotrypsin at pH 3. At small r, the approximate expressions overpredict the attraction. In agreement with the limitation imposed by the high-temperature approximation, significant divergence of the two models occurs when the potential of mean force exceeds about 1 kT. For the selected values of q and μ, the charge-dipole potential of mean force is far more attractive than the dipole-dipole potential. Thus, the high-temperature approximation fails at larger distances of separation for the charge-dipole potential relative to the dipole-dipole potential. For the dipole-dipole-interaction, the difference between the approximate analytical expression, Eq. [5], and the numerical integration of Eq. [2] is negligible at all distances, as shown in Figure 2(b).

Finite-Length Dipoles

Figures 3(a) and (b) show reduced finite-length dipole potentials of mean force as a function of separation distance, r, for two values of dipole length, L. Electrostatic parameters correspond to those of aqueous bovine α-chymotrypsin at pH 3, as in Figure 2. In proteins, the majority of the charged groups are located at the protein surface (10). Thus, we can approximate L as the protein diameter; for α-chymotrypsin $L = 43.4$ Å (11). The point charge, q', that corresponds to the observed dipole moment is obtained from the relation $\mu = q'L$. For α-chymotrypsin at pH 3, this gives $q' = \pm 2.9e$. For the point-dipole case, $L = 0$, numerical integration of Eqs. [1] and [2] was used to obtain potentials of mean force. Figure 3(a) shows that the point-dipole approximation underpredicts the finite-length charge-dipole attraction by about 20% near contact ($r = 43.4$ Å). For the charge-dipole interaction, the effect of a nonzero dipole length becomes insignificant at distances greater than $2L$. Figure 3(b) shows that the point-dipole model greatly underpredicts the attraction given by the finite-length dipole-dipole model. Near contact, the dipoles tend to align with $\theta_1 = \theta_2 = 0$ permitting the point charges of the two dipoles to approach contact. The resulting potential of mean force decreases rapidly and is singular as r approaches contact. However, at distances greater than $2L$ the effect of the dipole's charge separation is negligible.

IV. Discussion

Figures 2 and 3 show that the two assumptions made in the derivation of the approximate point-dipole expressions (Eqs. [4] and [5]) impart opposing deviations from the finite-length dipole results. The high-temperature approximation overpredicts, and the point-dipole approximation underpredicts the finite-length charge-dipole and dipole-dipole potentials of mean force. The approximate expressions are not valid for large values of the dipole moment or at small separation distances.

Proteins may have a layer of bound water associated at their surfaces (12) extending the effective diameter of the protein by as much as 6 Å (12, 13). In that event, the hard-sphere contact distance is greater than the length of the dipole, L. At this contact value of $r = 49.4$ Å, Figure 3 shows that the difference in using the finite-length dipole interaction compared to the point-dipole interaction is approximately 20% for the dipole-dipole interaction and about 10% for the charge-dipole interaction.

While the finite-length dipole model is useful for determining the effect of relaxing the point-dipole and high-temperature approximations, consideration of the internal dielectric constant of the protein may be important. For spherically-symmetric charge distributions, inclusion of the internal dielectric constant results in a small effect (8, 14), or no effect in the case of a completely uniform surface charge (6). For asymmetric charge distributions, however, Phillies (6) showed a significant increase in the attraction of both charge-dipole and dipole-dipole interactions when the internal dielectric constant is taken into account.

The simple model discussed here is limited to consideration of only individual electrostatic interactions (i.e., the interaction of a charge with a dipole or the interaction of a dipole with a dipole), because the angle-averaged electrostatic pair potentials are nonlinearly related and, thus, cannot be directly summed. Phillies has illustrated this nonlinearity (6). Phillies considered the potential energy between two charged point dipoles involving the interaction between two separate charge-dipole pairs (i.e., charge 1 with dipole 2, and charge 2 with dipole 1). The pair potentials are summed and then averaged over all configurations. The result is an orientationally-averaged charge-dipole pair potential that is four-fold greater than that given by Eq. [4], rather than two-fold greater as expected if the angle-averaged pair potentials were additive. For finite-length dipole interactions, all three charges (central net charge and two dipole charges) should be considered, and the orientational average taken subsequently. This would be a first step towards including the entire protein charge distribution and investigating the effects of specific charge interactions at the protein surface.

V. Conclusions

We have shown a simple method for calculating charge-dipole and dipole-dipole potentials of mean of force for finite-length dipoles. Comparison of pair potentials calculated for finite-length and point-dipoles using parameters for aqueous bovine α-chymotrypsin show that approximations inherent in the analytical point-dipole expressions may introduce significant errors.

Acknowledgments

The authors are grateful to the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of U.S. Department of Energy under Contract No. DE-AC03-76SF00098. For additional financial support, the authors are grateful to the National Science Foundation.

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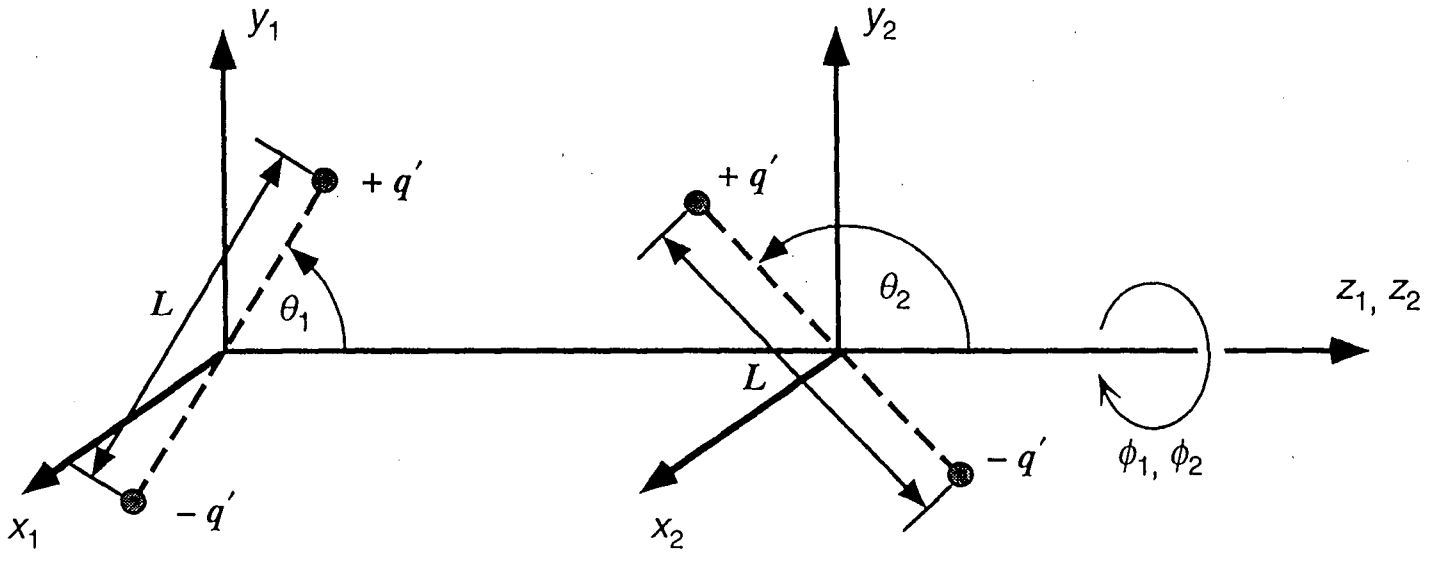
Figure Captions

Figure 1 Schematic of the interaction of two finite-length dipoles. Dipoles are represented as a pair of equal charges, $\pm q'$, separated by dipole length, L. The location of the dipoles is given by the center-to-center separation distance, r. Molecular orientation is described by two angles: θ from the axis to the dipole and ϕ from the plane of the page to the dipole. In the dipole-dipole interaction, angles ϕ_1 and ϕ_2 yield only one independent angle: $\phi_{21} = \phi_2 - \phi_1$. For the charge-dipole interaction, dipole 1 is replaced by a point charge at origin 1, and the value of ϕ_{21} becomes irrelevant.

Figure 2 Reduced point-dipole potentials of mean force for a) charge-dipole and b) dipole-dipole interactions. Analytical results are from Eqs. [4] and [5]. Numerical results are from integration of Eq. [3] for point-dipole expressions [1] and [2]. Electrostatic parameters are for aqueous α-chymotrypsin: μ = 381.5 Debye (1.273×10^{-17} C Å), $q = +14.2e$, and $\varepsilon_r = 78.54$. $T = 298$K. Contact occurs at r = 43.4 Å, corresponding to the diameter of α-chymotrypsin.

Figure 3 Reduced finite-length-dipole potentials of mean force for (a) charge-dipole and (b) dipole-dipole interactions. Results for $L = 0$ are from integration of Eq. [3] for point-dipole expressions [1] and [2] and are the same as the numerical results of Fig. 2. Results for L = 43.4 Å are from integration of Eq. [6]. Electrostatic parameters are for aqueous α-chymotrypsin: μ = 381.5 Debye (1.273×10^{-17} C Å), $q = +14.2e$, and $\varepsilon_r = 78.54$. $T = 298$K. Contact occurs at r = 43.4 Å, corresponding to the diameter of α-chymotrypsin.



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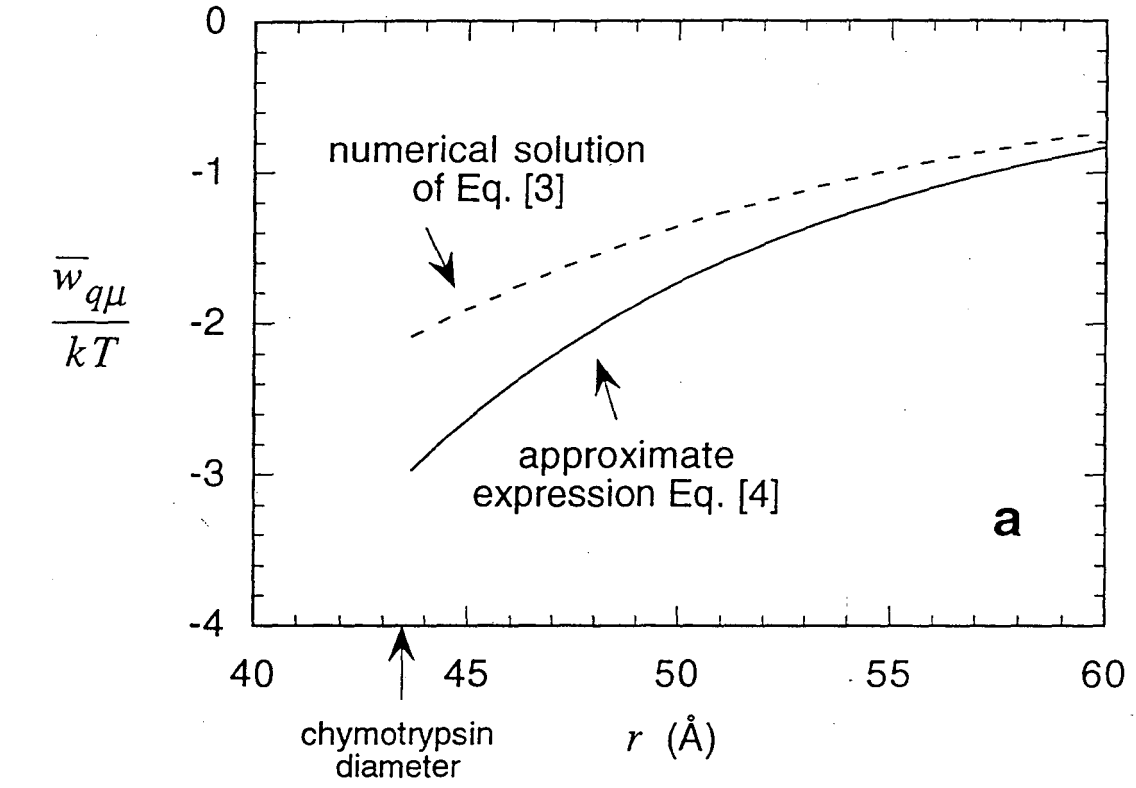
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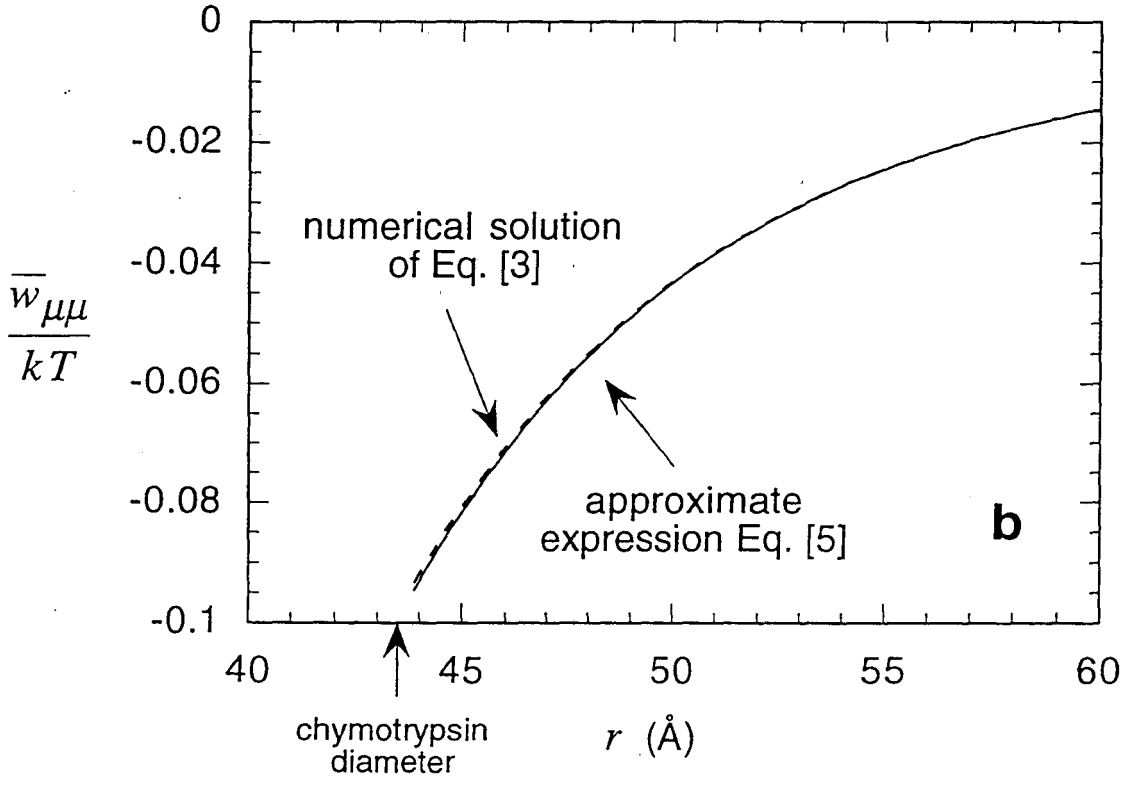
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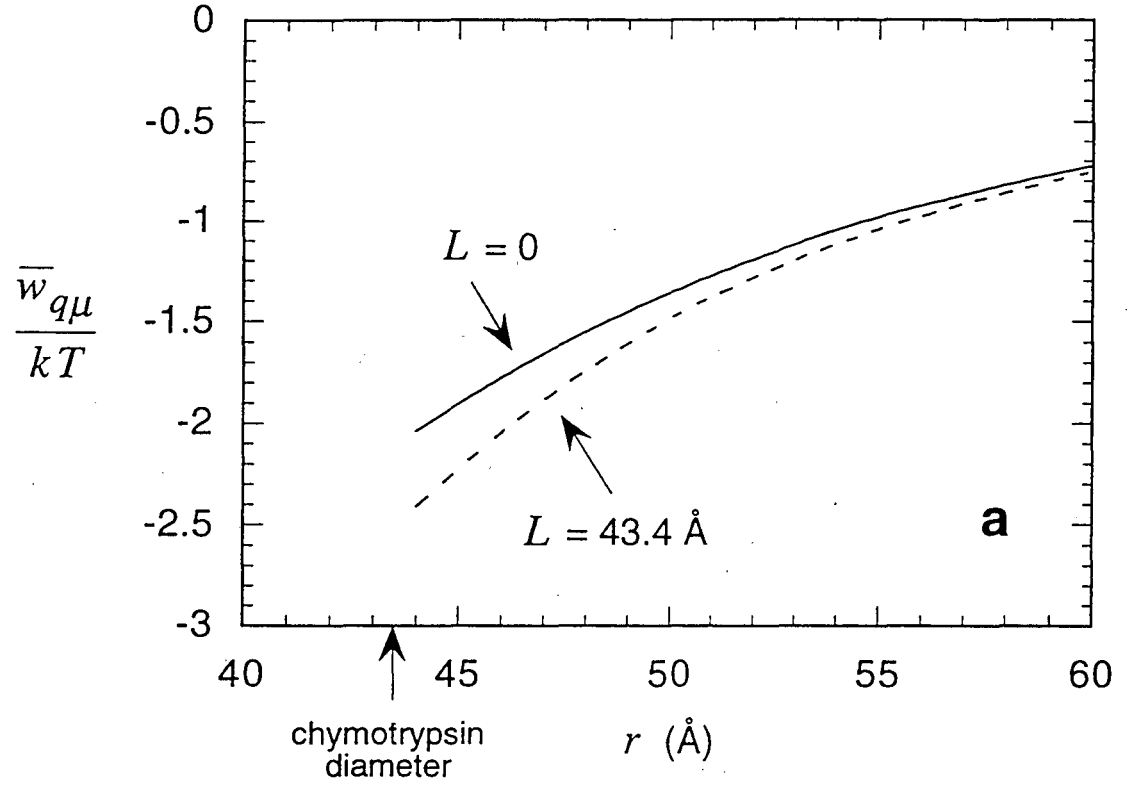
Figure 2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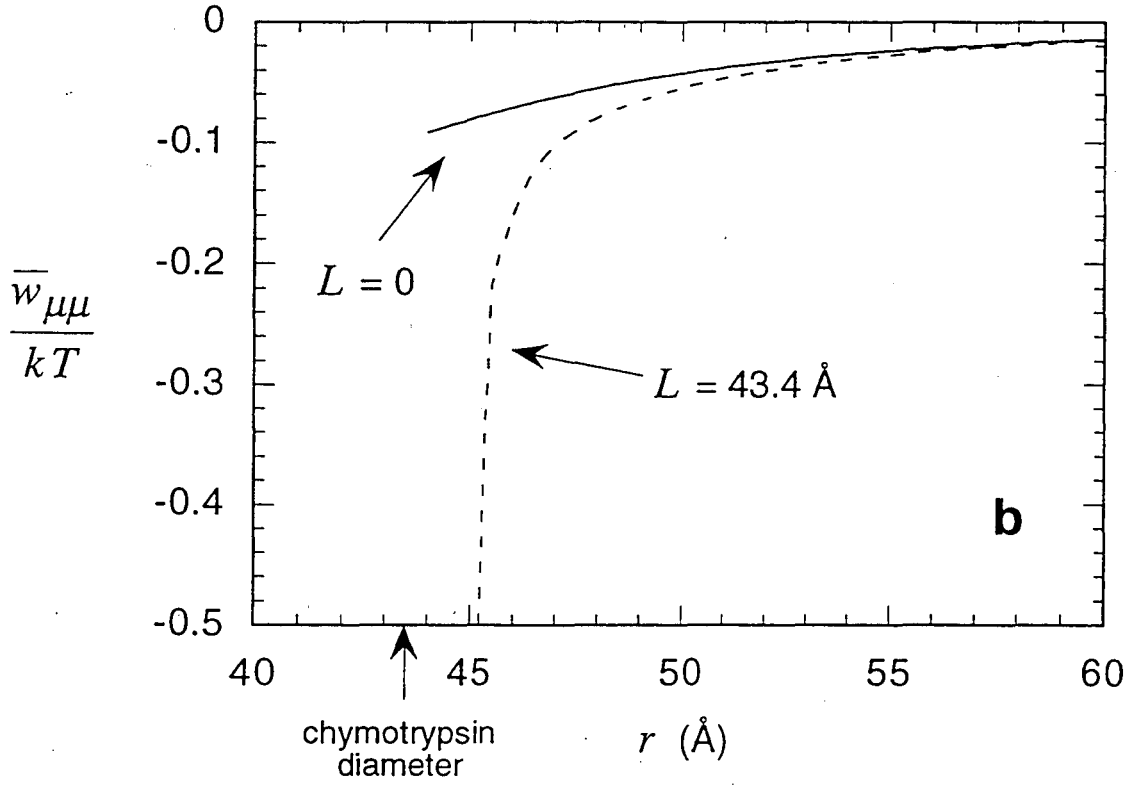
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chymotrypsin diameter
r (Å)

Figure 3

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UNIVERSITY OF CALIFORNIA
TECHNICAL INFORMATION DEPARTMENT
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