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Rotational friction on globular proteins combining dielectric and hydrodynamic effects

Arnab Mukherjee, Biman Bagchi *

Solid State and Structural Chemistry Unit, Indian Institute of Science, Bangalore 560 012, India

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Abstract

Rotational friction on proteins and macromolecules is known to derive contributions from at least two distinct sources – hydrodynamic (due to viscosity) and dielectric friction (due to polar interactions). In the existing theoretical approaches, the effect of the latter is taken into account by increasing the size of the protein with the addition of a hydration layer. Here, we calculate the rotational dielectric friction on a protein (ζ_{DF}) by using a generalized arbitrary charge distribution model (where the charges are obtained from quantum chemical calculation) and the hydrodynamic friction with stick boundary condition, by using the sophisticated theoretical technique known as tri-axial ellipsoidal method (ζ_{TR}). The calculation of hydrodynamic friction is done with only the dry volume of the protein (no hydration layer). We find that the total friction thus obtained by summing up ζ_{DF} and ζ_{TR}, gives reasonable agreement with the experimental results, i.e., $\zeta_{exp} \approx \zeta_{DF} + \zeta_{TR}$.

1. Introduction

In this Letter, we present an interesting result that the experimentally observed rotational correlation time of a large number of proteins can essentially be described as the combined effect of the rotational dielectric and hydrodynamic frictions on the proteins. Thus, one need not assume the existence of a rigid hydration layer around the protein, as is often assumed in the standard theoretical calculations of hydrodynamic friction.

The study of rotational friction of proteins in aqueous solution has a long history [1–9]. Despite many decades of study, several aspects of the problem remain ill understood. For proteins and macromolecules, the rotational friction is obtained from Debye–Stokes–Einstein (DSE) relation given by

$$\zeta_R = 8\pi\eta R^3, \tag{1}$$

where ζ_R is the rotational friction on the protein and R is the radius of the protein. The dielectric measurement of South and Grant [3] showed that the experimental value of rotational friction of myoglobin could only be explained by the above DSE equation if one assumes a thick hydration layer around the protein – thereby increasing the radius of the protein. It is well known that spherical approximation embedded in DSE is grossly in error [10] and the shape of the protein is quite important. However, even with the more recent advanced techniques such as tri-axial ellipsoid method [4] and the microscopic bead modeling technique [5,6], which take due recognition of the non-spherical shape of the macromolecule, agreement with the experimental result is not possible without the incorporation of a rigid hydration layer [7]. The importance of hydration layer is discussed in a recent paper by Zhou [11]. In the case of tri-axial ellipsoidal method, the values of the axes are increased proportionately by increasing the percentage of encapsulation of the protein atoms inside its equivalent ellipsoid [8,9]. On the other hand, the microscopic bead modeling technique uses beads of much

* Corresponding author.
E-mail address: bbagchi@sscu.iisc.ernet.in (B. Bagchi).

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bigger size [5] (3.0 Å instead of 1.2 Å) to take care of the effect of hydration layer. Without the hydration layer, the estimate of friction obtained from the theory is systematically lower.

It has been recognized quite early that water in the hydration layer surrounding proteins and macromolecules has completely different dynamical properties than those in the bulk [12]. Recent experimental and simulation studies have shown that the water in the surface of the protein exhibits bimodal dynamics [13]. Majority of the water molecules seem to retain their bulk-like dynamics while a fraction (~20%) exhibits markedly slow dynamics.

Recent solvation dynamics and photon echo peak shift experiment not only established the existence of slow water on the surface of proteins but also showed that the hydration layer is quite labile [14]. The labile hydration layer has been explained in terms of a dynamic exchange model [15], which is later confirmed by computer simulations [16].

The mode coupling theory (MCT) is another viable quantitative theory, which has been quite successful in describing translational and rational motion of small molecules [17]. This approach has also been extended to treat dynamics of polymer and biomolecules [18]. It was found in MCT that if one neglects the translational mode of the solvent molecules, then the friction on polar solute increases by several factors. Continuum models/hydrodynamic description of rotational friction always ignored this translational component. In fact, this translational component plays a hidden role in reducing the effect of the role of molecular level solute–solvent and solvent–solvent pair (both isotropic and orientational) correlations that increase the value of the friction over the continuum model prediction. Thus, the issue is rather involved. In fact, the continuum model is found to give accurate results due to cancellation of two errors: neglect of short-range correlations and neglect of translational contribution. In view of the above, it is thus important to note that the slow water molecules in the hydration layer can enhance the friction considerably. Thus, the classical picture of rigid, static hydration layer needs to be replaced by dynamic layer where the translational motion of the water molecules should be related to the residence time. However, only preliminary progress has been made in this direction. Thus, continuum models remain the only theoretical method to treat dielectric friction on complex molecules.

An important and nontrivial issue in the calculation of the rotational friction is that proteins are characterized by complex charge distribution. The earliest models to estimate the enhanced friction on a probe, due to the interactions of its polar groups with the surrounding water molecules in an aqueous solution, employed a point dipole approximation [19,20]. In the simplest version of the model, the probe molecule is replaced by a sphere with a point dipole at the *center* of the sphere. Such an approach is reasonable for small molecules, although continuum model itself may have certain limitations. The situation is quite different for large molecules like proteins because the charge here is distributed over a large volume and the surface charges are close to the water molecules. Thus, the point dipole approximation becomes inapplicable to such systems. This limitation of the early continuum models was removed by Alavi and Waldeck [21] who obtained an elegant expression for the dielectric friction on a molecule with extended arbitrary charge distribution. By studying several well-known dye molecules, they demonstrated that the extended charge distribution indeed has a strong effect on the dielectric friction on the probe molecules. The work of Alavi and Waldeck [21] constitutes an important advance in the study of dielectric friction. The role of dielectric friction has been studied for the organic molecules by other authors [22].

The objective of the present work is an attempt to replace the rigid hydration layer used in hydrodynamic calculation. To this goal, we calculate the hydrodynamic friction using the tri-axial method [4], in which the shape of a protein is mapped to an ellipsoid of three unequal axes – closely representing the shape and size of the protein. No hydration layer is added in the calculation. We then calculate the dielectric friction using Alavi and Waldeck's model of generalized charge distribution for a large number of proteins. The friction contributions obtained from the above two methods are combined to obtain the total rotational friction. When compared, the total friction has been found to agree closely with the experimental result.

We have also extended the work of Alavi and Waldeck to include multiple shells of water with different dielectric constants around a protein. The multiple shell model was introduced in concern with the experimental observation of varying dielectric constants of water from the hydration layer surrounding a protein to the bulk water. These shells have distinct dielectric properties – both static and dynamic. The resulting analytical expressions (not shown here) can be used to obtain quantitative prediction of the effects of a slow layer of water molecules on the dielectric friction on proteins. However, the multiple shell model in the continuum fails since it adds up the friction in every layer.

2. Results and discussion

Here, we discuss the results obtained from the different aspects of rotational friction of proteins. The coordinates of the proteins are obtained from protein data bank (PDB) [23].

2.1. Dielectric friction

Dielectric friction is an important part of rotational friction for polar or charged molecules in polar solvent, because of the polarization of the solvent medium. The solvent molecules, being polarized by the probe, create a reaction filed, which opposes the rotation of the probe.

Many of the amino acid residues, which constitute the protein, are polar or hydrophilic. Therefore, in the aqueous solution, a protein and other polar molecules experience significant dielectric friction. There exist several theories [19,20,24], which account for the dielectric contribution to the friction. Some of these theories are continuum model calculation of a point charge or point dipole rotating within the spherical cavity. Nee and Zwanzig [19] provide an estimate of dielectric friction on a point dipole in terms of the dipole moment of the point dipole, dielectric constant of the solvent, Debye relaxation time, and the chosen cavity radius. Later, Alavi and Waldeck [21] extended this theory to incorporate the arbitrary multiple charge distribution of the probe molecule.

The dielectric friction on the proteins has been calculated from the expression of Alavi and Waldeck for arbitrary multiple charge distribution model given below [21]

$$\zeta_{\mathrm{DF}} = \frac{8}{R_{\mathrm{c}}}\frac{\epsilon_{\mathrm{s}}-1}{(2\epsilon_1+1)^2}\tau_{\mathrm{D}}\sum_{j=1}^{N}\sum_{i=1}^{N}\sum_{l=1}^{\infty} \times \sum_{m=1}^{l}\left(\frac{2l+1}{l+1}\right)\frac{(l-m)!}{(l+m)!}q_i q_j\left(\frac{r_i}{R_{\mathrm{c}}}\right)^{l}\left(\frac{r_j}{R_{\mathrm{c}}}\right)^{l} \times m^2 P_l^m(\cos\theta_i)P_l^m(\cos\theta_j)\cos(m\phi_{ji}), \quad (2)$$

where R_{c} is the cavity radius, (r_i, θ_i, ϕ_i) is the position vector and q_i is the partial charge of the ith atom. $P_l^m(\cos(\theta_i)$ is the Legendre polynomial. The maximum value of l used in the Legendre polynomial is 50. ϵ_{s} is the static dielectric constant of the solvent. Since the solvent here is water, ϵ_{s} is taken to be 78 and the Debye relaxation time τ_{D} is taken as 8.3 picosecond (ps). The cavity radius R_{c} is chosen such that the ratio of the longest bond vector of the protein to R_{c} is 0.75.

The partial charges (q_i) of the atoms constituting the proteins have been calculated using the extended Huckel model of the semi empirical calculation package of Hyperchem software. The dielectric friction is calculated on each of the atoms in a protein. The rotational frictions around X, Y and Z direction are calculated by changing the labels of the atom coordinates. The average dielectric constant $\zeta_{\mathrm{DF}}^{\mathrm{av}}$ is the harmonic mean of the dielectric frictions along X, Y and Z direction. Here, X, Y and Z denote the space fixed Cartesian coordinate of the proteins, as obtained from PDB [23].

2.2. Hydrodynamic friction

The hydrodynamic rotational friction of the protein depends on its shape and size. Hydrodynamic friction was estimated earlier by the well-known DSE relation (Eq. (1)). Perrin in 1936 [25], extended the DSE theory to calculate the hydrodynamic friction for molecules with prolate and oblate like shapes. Both prolate and oblate have two unequal axes. Harding [4] further extended the theory to calculate the hydrodynamic friction using a tri-axial ellipsoid. All the above theories employ stick binary condition to obtain the hydrodynamic friction.

Tri-axial ellipsoidal technique requires the construction of an equivalent ellipsoid of the protein. We have followed the method of Taylor et al. [26] to construct an equivalent ellipsoid from the moment matrix. The eigenvalues of this equivalent ellipsoid are proportional to the square of the axes. So this method provides with the two axial ratios. We then obtained the values of the axes using the formula given by Mittelbach [27]

$$R_\gamma^2 = \frac{1}{5}(A^2+B^2+C^2), \quad (3)$$

where R_γ is the radius of gyration and A, B and C are the three unequal axes of a particular protein.

Once the protein is represented as an ellipsoid with three principle axes, the hydrodynamic friction is calculated using Hardirig's method [4,28]. $\zeta_{\mathrm{TR}}^{\mathrm{av}}$ is harmonic average of the hydrodynamic friction with respect to three principle axes of the ellipsoid.

2.3. Total rotational friction: comparison with experimental results

We define the total rotational friction as the sum of dielectric friction ($\zeta_{\mathrm{DF}}^{\mathrm{av}}$) and the hydrodynamic friction without the hydration layer (i.e., tri-axial friction, $\zeta_{\mathrm{TR}}^{\mathrm{av}}$) as given below

$$\zeta_{\mathrm{total}} = \zeta_{\mathrm{DF}}^{\mathrm{av}} + \zeta_{\mathrm{TR}}^{\mathrm{av}}. \quad (4)$$

In Table 1, we have shown the values of the average dielectric ($\zeta_{\mathrm{DF}}^{\mathrm{av}}$), hydrodynarnic ($\zeta_{\mathrm{TR}}^{\mathrm{av}}$) friction. Total friction (ζ_{total}) defined above is shown in the fourth column. To compare with the experimental results, we have shown the experimental values of the rotational friction in the next column. Note here, while the total friction, which is the contribution from both dielectric and hydrodynamic friction, is close to the experimental result, the microscopic bead modeling predicts the result, which is close to experimental value by itself [6,10].

Note that the values obtained from the tri-axial method are much lower than the experimental values. Here, we can talk about an important aspect of standard hydrodynamic approach – hydration layer. One

Table 1
Comparison between the total friction and the experimental results

Protein	PDB id	ζ_{DF}^{av}	ζ_{TR}^{av}	ζ_{total}	ζ_{exp}
Bovine pancreatic trypsin inhibitor	6pti	16.0	73.1	89.1	96.8
Calbindin D9k, holo form	Iig5	39.5	78.6	118.1	125.0
Human ubiquitin	lubq	19.3	83.8	103.1	118.9
Ferricytochrome C_{551}	351c	44.5	82.2	126.7	130.1
Plastocyanin, Cu(II) form	Ipcs	65.7	96.6	162.3	149.5
Oncogenic protein $pl3^{MTCP1}$	lalx	59.3	129.9	189.2	241.9
Binase	Igou	63.5	127.7	191.2	191.3
Ribonuclease A	laqp	68.0	150.1	218.1	186.1
Azurin, Cu(I) form	Ie5y	84.7	133.4	218.1	190.4
Hen egg-white lysozyme	Ibwi	77.8	135.7	213.5	203.6
Bovine-lactoglobulin, monomer	Ib8e	112.0	172.6	284.6	270.6
Adenylate kinase, apo form	4ake	110.7	376.1	486.8	478.2
Bovine ribonuclease A	3rn3	80.5	145.1	225.6	235.0
Sperm whale myoglobin	Imbn	164.3	183.1	347.4	246.3

Results are given in the unit of 10^{-23} erg s.
The references to the experimental results of rotational diffusion of the corresponding proteins are given in Ref. [10].

finds that hydrodynarnic values of rotational friction underestimate the rotational friction unless the effect of hydration layer is taken into account. However, the effect of hydration layer is usually incorporated in an ad hoc manner, by increasing the percentage of encapsulation of the atoms inside the ellipsoid [8,9]. In this method, once the two axial ratios are obtained from the equivalent ellipsoid, the actual values of the axes are obtained by increasing the encapsulation of the protein atoms inside the ellipsoid. In the calculation presented here, the axes are obtained by equating with the radius of gyration (Eq. (3)). Therefore, we considered *no hydration layer* in this calculation of hydrodynamic friction.

The similarity between the total friction and the experimental friction is shown in Fig. 1, where we have plotted the experimental values of rotational friction against the total friction for a large number of proteins. For most of the proteins, the results fall on the diagonal line.

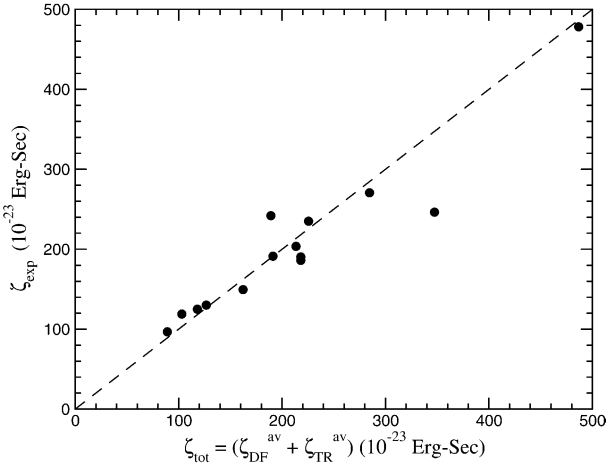

Fig. 1. The combined friction from hydrodynamic and dielectric is plotted against the experimental results. The dashed line shows the diagonal to guide the eye.

From the results shown in Table 1 and Fig. 1, we can conclude that the sum of dielectric friction and the hydrodynamic friction of the dry protein is approximately equal to the experimental result. So the effect of hydration layer comes here from the dielectric friction contribution.

$$\zeta_{total} \approx \zeta_{exp}. \tag{5}$$

3. Conclusion

Let us first summarize the main results of this work. We have calculated the hydrodynamic rotational friction on proteins using the tri-axial ellipsoid method, formulated by Harding [4], and the dielectric friction using the generalized charge distribution model derived by Alavi and Waldeck [21]. The hydrodynamic friction is calculated without the inclusion of any hydration layer. We have found that the combined effect of dielectric and hydrodynamic friction gives an estimate close to the experimental result. This approach seems to provide a microscopic basis for the standard hydrodynamic approach, where a hydration layer is added to the protein to calculate the rotational friction.

The calculations adopted here are still not without limitations. The continuum calculation of dielectric friction is dependent on the assumed cavity radius. Unfortunately, there is yet no microscopic basis to assume certain value of the cavity radius for the calculation of dielectric friction. Moreover, the effect of increasing dielectric constant of the solvent from the vicinity of the protein to the bulk is not taken into account by Alavi and Waldeck [21]. Thus, we have attempted to incorporate a multi shell model to incorporate multiple shells with varying dielectric constants. The drawback of incorporation of multiple shells in the continuum is that the frictional contributions from each of the shells

add up, thereby giving rise to an unphysical large result.

Similarly, the tri-axial method and bead modeling method suffer from the lack of microscopic basis to determine the exact values of the axes and the bead size, respectively.

A potentially powerful approach to the problem is the mode coupling theory [29,30], which uses the time correlation formalism to obtain the memory kernel of the rotational friction.

$$\Gamma_{\mathrm{s}}(z) = \Gamma_{\mathrm{bare}} + \mathscr{A}\int_0^\infty \mathrm{e}^{-zt}\int_0^\infty \mathrm{d}k\, k^2 \sum_{l_1 l_2 m} c^2_{l_1 l_2 m}(k) F_{l_2 m}(k,t) \tag{6}$$

$$\Gamma_{\mathrm{c}}(z) = \Gamma_{\mathrm{bare}} + \mathscr{A}\int_0^\infty \mathrm{e}^{-zt}\int_0^\infty \mathrm{d}k\, k^2 \times \sum_{l_1 l_2 m} F^{\mathrm{s}}_{l_1 m}(k,t) c^2_{l_1 l_2 m}(k)\, F_{l_2 m}(k,t), \tag{7}$$

where $A = \frac{\rho}{2(2\pi)^4}\cdot c_{l_1 l_2 m}$ is the $l_1 l_2 m$th coefficient of the two particle direct correlation function between any two dipolar molecules. $F^{\mathrm{s}}_{l_1 l_2 m}$ and $F_{l_2 m}(k,t)$ are the single particle and the collective orientational correlation functions, respectively.

Eqs. (6) and (7) are the standard mode coupling theory expressions for rotational friction, which has to be solved self consistently.

The advantage of the mode coupling approach is that the once the charge density of the protein molecules and the dipole density of the water molecules surrounding the protein are defined, the rotational friction can be obtained in terms of the direct correlation function and the static and dynamic structure factors of the protein-water systems. These are again related by Ornstein–Zernike equation [31].

The important aspect of this microscopic theory of dielectric friction is the hidden contribution of the translational modes. In the hydration layer, the rotational friction is enhanced due to the slow translational component. This effect of translation could not be approached through continuum calculation. Work in this direction is under progress.

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