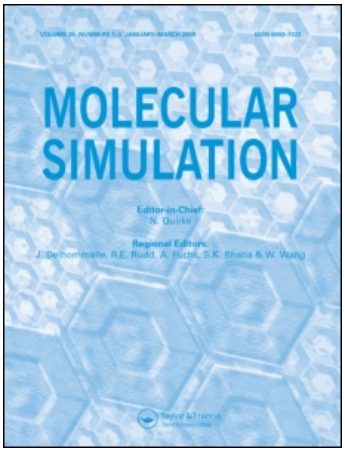

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Classical Molecular Dynamics Simulation of Kappa Squared Factor in Resonance Energy Transfer for Linear Dipole Models

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Molecular dynamics simulations of linear models interacting through a dipolar Kihara intermolecular potential are presented. Molecular orientation correlations are used to calculate the orientational factor kappa squared in the resonance energy transfer (RET) as a function of the intermolecular separation. The distance, R_0(2/3), at which the simulated systems show an isotropic behavior is calculated and an analysis of the dependence of R_0(2/3) on microscopic properties (molecular aspect ratio and dipole moment) as well on thermodynamics (temperature and density) is presented. An explanation of the use of metallic cations as probes in RET is given and some relations of our models with biological molecules are pointed out.

Keywords: Molecular dynamics simulation; kappa squared factor; resonance energy transfer; linear dipole models

INTRODUCTION

Resonance energy transfer (RET) is the radiationless transmission of an energy quantum from its site of absorption, usually called the donor, to another specific site, usually called the acceptor, in a molecule or system of molecules [1,2]. The theory of RET is universally attributed to Förster [3]. RET occurs simultaneously with diffusion processes over distances greater than interatomic without kinetic collision. RET is called homotransfer when the molecules involved are identical or heterotransfer when the molecules are different. Although, heterotransfer is more used among biochemists or biophysicists, we consider here only homotransfer as a first step in our study. Molecular orientations of dipoles of donor and acceptor are implied in the RET in a nontrivial way. One of the most elusive factors intervening in RET is an intermolecular quantity depending on mutual orientations commonly known as kappa squared (κ^2). This factor is related to the orientation correlation between donor and acceptor dipole moments and several different statistical approaches [4–6] have been used to obtain κ^2. Moreover, important experimental [7] and theoretical [8] contributions have been made to relate RET to the molecular length of the donor or the acceptor. However, we are not aware of any systematic simulation study to link κ^2 to microscopic properties, essentially molecular shape and dipole moment, μ, but also to thermodynamic properties: density d, and temperature T. The main goal of this work is to make a contribution to filling this void. Our point of departure is the relation between κ^2 defined as an angular average and the coefficients of the pair correlation function (PCF) of a fluid system in an expansion in spherical harmonics. Exploiting this relation, we present here a classical scheme to calculate κ^2 for linear rod models representing linear or pseudolinear molecules [9]. We use the so-called Kihara intermolecular potential which explicitly depends only on the shortest distance between rods plus a dipole placed on the model center and aligned along the molecular axis (see Fig. 1). We have previously obtained the vapor–liquid equilibrium (VLE) curve for this kind of system [10] and we

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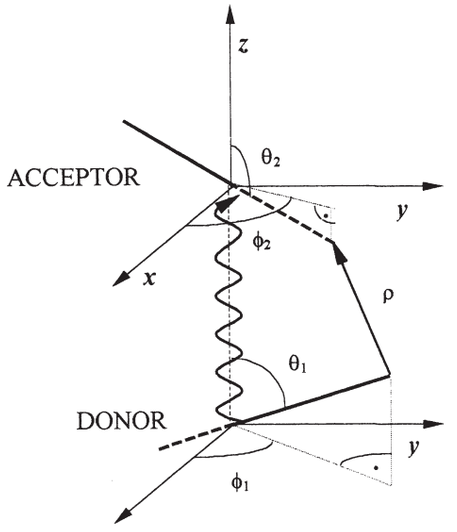

FIGURE 1 The reference framework for the models considered in this work.

simulate at these equilibrium states for the shortest aspect ratios. Furthermore, we also study here models of very high length/breadth ratio at low densities because these states are closer to the relevant biological conditions. In all cases, we calculate the distance $R_0(2/3)$ at which κ^2 reaches the value of 2/3. This value is often identified with R_0, the Förster distance at which RET is 50% of its total value.

Two general criticisms may be leveled at our work [11]:

First, we are simulating systems composed of particles moving and rotating without restrictions in a three-dimensional (3D) space. However, molecules used as probes in RET are often covalently bound to a macromolecule. Thus, its movement is always related to the macromolecule. Indeed, an accurate knowledge of κ^2 for a given system, would require the simulation of the complete system: probe + macromolecule. However, our system is not so artificial as one could think because the macromolecule and the probe move and rotate in the three-dimensional space as a whole. So, the hypothesis of always taking $k^2 = 2/3$ is even more unjustified for the complete system than for the isolated probe. We analyze this point deeper in the text below.

The second criticism is that the exact value of κ^2 is irrelevant because κ^2 varies very slowly with R and the limit value can always be taken confidently. We will show that is true only beyond a minimum value of R when the variation of κ^2 is really very slow. Fortunately, most of the assigned distances in biological molecules are greater than this limit. However, κ^2 values at short distance may be required in some cases. Furthermore, the distance between sites in a protein can vary appreciably during a chemical reaction as folding or unfolding. In this case, neither the use of a limit nor a constant value for κ^2 may be adequate. However, few authors seem to be aware of this problem [12]. A second goal of this work is to demonstrate the necessity of using variables values of κ^2 to analyze RET in a reaction mixture. Indeed, a recent paper [13] considers the time anisotropy of κ^2 and can be seen as the dynamic counterpart of the work presented here.

The best-known example of homotransfer of an approximately linear molecule is retinal, an aldehyde participating in the vision process and often used as a probe in the study of biomembranes [14,15]. In what follows, we present a short discussion supporting the straightforward use of the isotropic value of 2/3 for κ^2 in this case. Finally, we present an example where κ^2 cannot be taken as a constant value because it changes during a protein folding/unfolding kinetic process.

RESONANCE ENERGY TRANSFER AND INTERMOLECULAR DIPOLE CORRELATION

The RET at an intermolecular separation R can be written as [1]

$$E(R) = \frac{R_0^6}{R_0^6 + R^6} \tag{1}$$

where R_0 is the so-called Förster distance given by

$$R_0^6 = \frac{9000 \ln(10) \kappa^2 Q_D J}{128 \pi^5 n^4 N_{Av}} \tag{2}$$

According to Eq. (1), the energy transfer is 50% at the Förster distance. Q_D is the quantum yield of the donor in the absence of acceptor molecules, J the overlap integral between donor emission spectrum and acceptor absorption spectrum, n the index of refraction of the medium, N_{Av} the Avogadro's number. κ^2 (kappa squared) is related to the mutual orientations of donor and acceptor (see Fig. 1) by

$$\kappa^2 = (\cos \gamma_{12} - 3 \cos \theta_1 \cos \theta_2)^2 \tag{3}$$

where

$$\cos \gamma_{12} = \cos \theta_1 \cos \theta_2 + \sin \theta_1 \sin \theta_2 \times \cos(\phi_1 - \phi_2) \tag{4}$$

The PCF of the linear molecules in a fluid system can be expanded as a series of double products of spherical harmonics of orientation angles [16]

$$g(\mathbf{r}, \theta_1, \theta_2, \phi_1, \phi_2) = \sum_{l,l',m} g_{l,l',m}(r) Y_{l,m}(\theta_1, \phi_1) Y^*_{l',m}(\theta_2, \phi_2) \tag{5}$$

where $Y_{l,m}(\theta, \phi)$ is a spherical harmonic and the asterisk refers to its complex conjugate.

Spherical harmonic coefficients, $g_{l,l',m}$ can be obtained during a Monte Carlo or Molecular Dynamics simulation as ensemble averages. Explicitly, equations giving the first l and l' odd coefficients are given by

$$g_{110}(r) = \iiint g(\mathbf{r}, \theta_1, \theta_2, \phi_1, \phi_2)\cos(\theta_1) \times \cos(\theta_2)\,\mathrm{d}\cos(\theta_1)\,\mathrm{d}\cos(\theta_2)\,\mathrm{d}\phi \quad (6)$$

$$g_{111}(r) = \iiint g(\mathbf{r}, \theta_1, \theta_2, \phi_1, \phi_2)\cos(\theta_1)\cos(\theta_2) \times \sin(\phi_1 - \phi_2)\,\mathrm{d}\cos(\theta_1)\,\mathrm{d}\cos(\theta_2)\,\mathrm{d}\phi \quad (7)$$

where the integral over the set of orientation angles, $\Omega = \{\theta_1, \theta_2, \phi\}$, is normalized to 1.

These coefficients vanish in the case of a nonpolar system, but not for a system containing dipoles. In this case, it is usual to define

$$h^{112}(r) = g_{110}(r) + g_{111}(r) = \int (I_{110} + I_{111})\,\mathrm{d}\Omega \quad (8)$$

where $I_{ll'm}$ are the functions under the integral sign in Eqs. (6) and (7).

On the other hand, if the system is isotropic κ^2 can also be obtained from an ensemble average. Moreover, if the dipole moments of donor and acceptor do not change during the transfer, then the definition of κ^2 is closely related to these angular coefficients. From Eqs. (3) and (4), we obtain:

$$\kappa^2 = \int (I_{110} + I_{111})^2\,\mathrm{d}\Omega \quad (9)$$

Thus, the angular coefficients of the expansion of PCF in spherical harmonics and κ^2 can be obtained simultaneously in a simulation. Note that κ^2 is indeed a function of r and not a constant.

To model the intermolecular interactions, we have chosen the Kihara potential. This particular intermolecular potential depends only on the shortest distance between molecular cores (see Fig. 1). Therefore, the potential seems to be very suitable to study the RET which is usually established in similar terms of the distance geometry [17]. Explicitly, Kihara potential is given by

$$u_{12}^{\mathrm{K}} = 4\varepsilon[(\sigma/\rho)^{12} - (\sigma/\rho)^6] \quad (10)$$

where ε and σ are parameters with energy and length dimensions, respectively, and ρ the shortest distance between molecular cores. ρ depends on the separation between molecular centers of mass and on mutual orientations but we simply write ρ for sake of clarity. The molecular core is a rod of length L in all the cases considered here. The reduced length of this rod is $L^* = L/\sigma$ for models. The total intermolecular potential is given by

$$u = u_{12}^{\mathrm{K}} + u^{\mu\mu} \quad (11)$$

where $u^{\mu\mu}$ is the dipole interaction energy. We take dipoles as point dipoles and this term is given by

$$u^{\mu\mu} = \frac{\mu_1\cdot\mu_2}{r^3} - \frac{3\cdot(\mu_1\cdot\mathbf{r})\cdot(\mu_2\cdot\mathbf{r})}{r^5} \quad (12)$$

This equation becomes still simpler if the dipole is placed on the molecular center of mass and the direction of dipole moment vector is along the rod axis

$$u^{\mu\mu} = \frac{\mu_1\cdot\mu_2}{r^3} - \frac{3\cdot(\mu_1\cdot r)\cdot(\mu_2\cdot r)}{r^5} = \frac{\mu^2}{r^3}\cdot(\cos\gamma_{12} - 3\cos\theta_1\cos\theta_2) \quad (13)$$

Note that the parenthesis term is just the squared root of the right-hand term in Eq. (3). Namely, κ has the meaning of the ensemble average of orientations for the intermolecular dipole interactions. Clearly, this interaction depends on the intermolecular separation unless the molecules are far apart.

We have previously determined the VLE for some of the less elongated models [10] presented here and we have performed simulations at some equilibrium states for the shortest models. However, these equilibrium densities correspond to unphysical states for the longest aspect ratios [18] and we have rather simulated at the same packing fraction, y, for the highest aspect ratios

$$y = d\cdot V_{\mathrm{m}} \quad (14)$$

where $V_{\mathrm{m}} = \pi\sigma^3(1 + 3L^*/2)/6$ is the molecular volume.

In this way, we are closer to the usual biological conditions. We have also monitored orientation parameters in these cases to be sure that we are in an isotropic phase.

MD simulations were carried out in the NVT-ensemble using a box containing 256 particles of reduced length L^* and a leap-frog algorithm to integrate the motion equations [19]. The integration time step, was set up as $\delta t^* = 3.5\times10^{-3}$. The reduced unit time is defined as $t^* = (M\sigma^2)^{1/2}/\varepsilon$, M being the molecular mass. Our runs consisted of 5000 steps for equilibration and 100,000 additional steps to calculate the averages. The Kihara potential makes no assumption about the mass distribution along the rod [20]. Here, we considered the rods as homonuclear diatomic molecules where half of the total mass is situated on each extreme of the rod. So, the reduced inertia momentum is $I^* = I/M\sigma^2 = L^{*2}/4$. κ^2 is written as a combination of spherical harmonics of PCF is strictly independent of mass distribution as other thermodynamic functions [21,22].

TABLE I Förster distances as function of molecular and thermodynamic properties

L^*	μ^{*2}	T^*	n^*	y	Φ	$R_0(2/3)/\sigma$
0.3	0.76	1.04414	0.39980	0.3035	1.0386	3.78
	0.76	1.04414	0.54494	0.4137	1.3246	3.53
	0.76	0.7541	0.54494	0.4137	1.4942	3.53
	1.5	1.089	0.415	0.3151	1.0591	3.73
	1.5	1.089	0.548	0.4160	1.3202	3.52
	1.5	0.786	0.548	0.4160	1.4958	3.52
	3.0	1.228	0.409	0.3105	1.0543	3.64
	3.0	1.228	0.555	0.4213	1.3039	3.50
	3.0	0.887	0.555	0.4213	1.4651	3.50
0.6	0.99	0.93729	0.30547	0.3039	1.1490	3.83
	0.99	0.93729	0.42244	0.4203	1.2643	3.43
	0.99	0.6769	0.42244	0.4203	1.3899	3.47
	2.0	0.9808	0.3195	0.3179	1.1284	3.71
	2.0	0.9808	0.4237	0.4215	1.2373	3.47
	2.0	0.7083	0.4237	0.4215	1.3704	3.42
	4.0	1.103	0.3193	0.3177	1.1103	3.76
	4.0	1.103	0.4305	0.4283	1.1875	3.45
	4.0	0.797	0.4305	0.4283	1.2985	3.45
0.8	1.15	0.8923	0.27626	0.3182	1.2052	4.01
	1.15	0.8923	0.37435	0.4312	1.2271	3.50
	1.15	0.6444	0.37435	0.4312	1.3505	3.50
	2.3	0.923	0.279	0.321	1.1718	3.82
	2.3	0.923	0.375	0.432	1.1853	3.49
	2.3	0.666	0.375	0.432	1.2909	3.49
	4.6	1.060	0.273	0.314	1.0784	3.75
	4.6	1.060	0.378	0.435	1.0932	3.46
	4.6	0.762	0.378	0.435	1.1761	3.51
1.5	1.7016	0.8923	0.0233	0.0397	3.7458	9.46
	1.7016	0.8923	0.0368	0.0626	3.4029	7.92
2	2.094	0.8923	0.01899	0.0398	4.0293	9.78
	2.094	0.8923	0.02992	0.0627	3.8483	7.98
3.5	3.2724	0.8923	0.01215	0.0398	5.5449	10.14
	3.2724	0.8923	0.01914	0.0626	4.5695	8.01
5	4.45	0.8923	0.00897	0.0399	7.3406	10.11
	4.45	0.8923	0.01414	0.0629		
	6.0426	7.35				

We also define the reduced dipole density, m, as

$$m^2 = \frac{\mu^2}{\varepsilon \cdot V_m} \tag{15}$$

because molecular properties follow approximately a corresponding states law when this definition is used [10].

RESULTS

We have performed simulations for systems at the thermodynamic states shown in Table I for different values of L^* ranging from 0.3 to 5 each in combination with different dipole moment values. These values have been chosen in most of cases to give the same reduced dipole densities [10] for different aspect ratios. The results of our simulations are shown in Figs. 2–5, where κ^2 is shown as a function of R/σ. Considering all the figures and especially Fig. 2, an appealing observation is that κ^2 goes to 2/3 in two different ways. At low densities and relatively high temperatures, κ^2 decays monotonically in an approximately exponential way. In other cases, κ^2 behaves as a damped oscillatory function. Both these behaviors have been well described for the radial distribution function of monatomic fluids [23]. In this case, there is one line, the Fisher–Widom line, separating the regions of damped oscillations and exponential decays. Our simulations suggest that a similar line may exist for the angular average defining κ^2. It is also apparent from Fig. 3 that κ^2 depends more strongly on density than on temperature, except at very low densities (Fig. 4). The dependence on the reduced dipole density is also weaker than on density, but note in Fig. 5 that a marked shoulder appears at short distances. That unexpected feature becomes nearly a

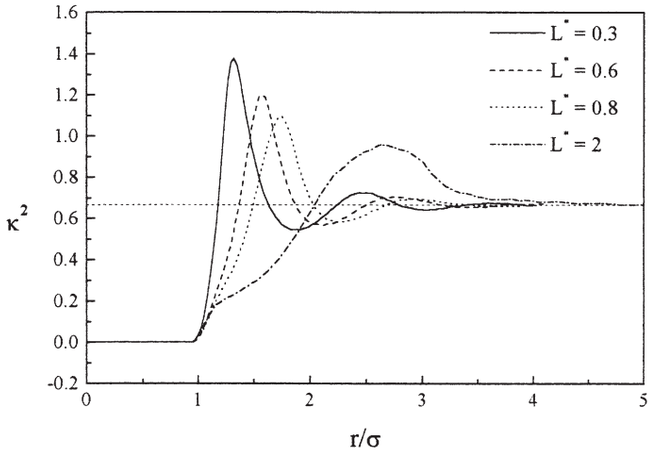

FIGURE 2 Angular average defining kappa squared for a system of linear molecules at different aspect ratios. The shown lines correspond to the thermodynamic state at the lowest density and highest temperature in Table I for each elongation. Reduced density dipole equals to 1 in all the cases.

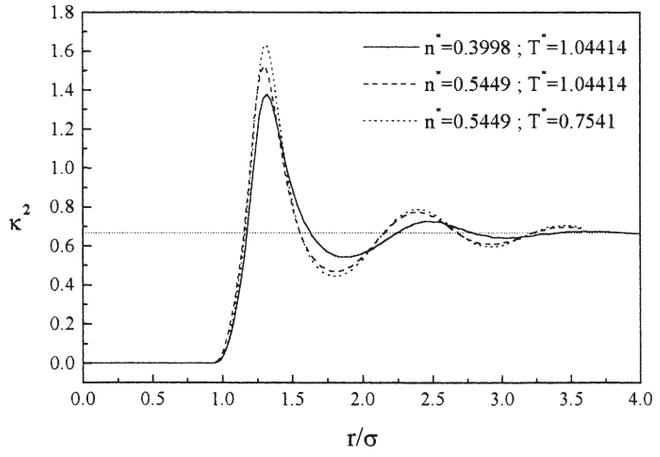

FIGURE 3 Angular average defining kappa squared for a system with $L^* = 0.3$ and $m^2 = 1$ for the thermodynamic states marked on the plot.

plateau at relatively low values of m^2 and corresponds to a nearly constant value of κ^2 at low distances but this value is clearly different from 2/3.

An important quantity coming from simulations is $R_0(2/3)$, i.e. is the distance where κ^2 reaches a value of 2/3 corresponding to a fully isotropic case [2]. Due to the asymptotic behavior of κ^2, it is not possible to ascertain when the limit value is reached in an unambiguous way. Here, we have used an integral criterion relating $R_0(2/3)$ to the area under a positive function built from κ^2 versus r plot. This function is defined as

$$\Phi = \int |(\kappa^2(r) - 2/3)r^2| \, dr \tag{16}$$

where the vertical bars mean absolute value. $R_0(2/3)$ is estimated as the upper limit that gives a value of Φ less than 1% apart from the total Φ value. Obviously, this definition is useful only when κ^2 has nearly reached its asymptotic value of 2/3. Values for Φ are given in Table I.

Experimental errors in the determination of R_0 from RET are frequently of the order of 20% or more. Values of $R_0(2/3)$ obtained with this method are shown in Table I. In all the cases, $R_0(2/3)$ is always much larger than intermolecular distances as RET requires. Indeed, it is little surprising that RET may occur even for very short linear models. We come back to this point below. Furthermore, it is evident from Table I that $R_0(2/3)$ hardly depends on the molecular geometry at least for not very different aspect ratios. With respect to the thermodynamic properties, clearly $R_0(2/3)$ decreases as the density increases and a good linear relationship between $R_0(2/3)$ and y^{-1} is shown in Fig. 6. However, $R_0(2/3)$ seems to be rather insensitive to the temperature and to the strength of dipole moment except at very high aspect ratios. All these observations agree with our intuition that energy should be transferred to longer distances when the density decreases and when molecules are longer. More surprising is that $R_0(2/3)$ is approximately independent of dipole moment.

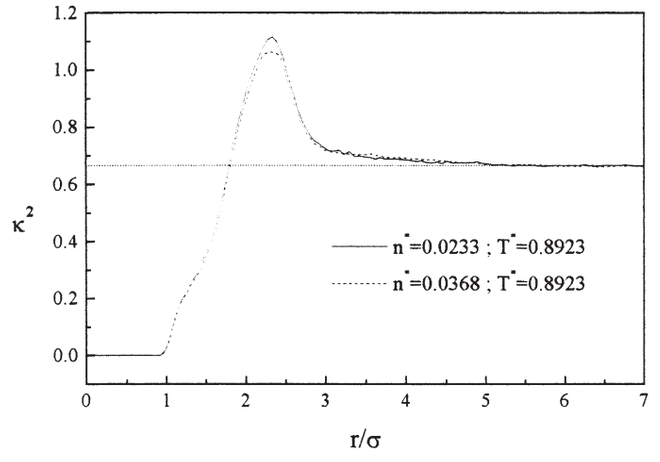

FIGURE 4 Angular average defining kappa squared for a system with $L^* = 1.5$ and $m^2 = 1$ at $T^* = 0.8923$ and very low densities.

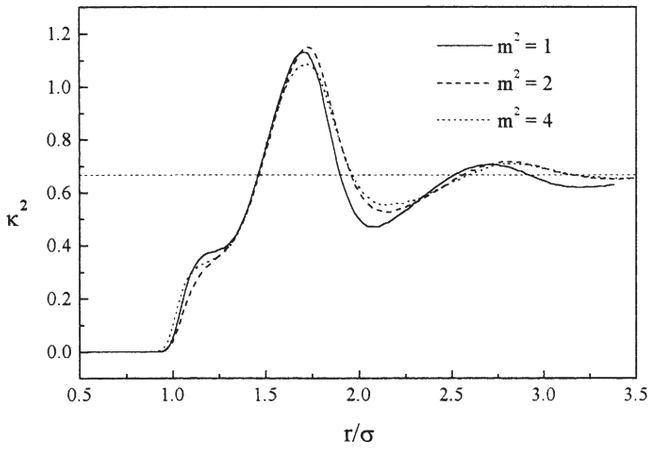

FIGURE 5 Angular average defining kappa squared for a system with $L^* = 0.8$ and different reduced dipole density at the thermodynamic states of lowest density and highest temperature in Table I.

Indeed, values of $R_0(2/3)$ are the same within the simulation error for states with close densities and very different dipoles in practically all the cases shown on Table I. This fact suggests that RET is strongly mediated by the dielectric constant of the environment in a nontrivial way, specially for shortest models. An additional remarkable feature is that $R_0(2/3)$ is non-zero even for $L^* = 0$, namely for a Stockmayer potential. This observation is in agreement with the fact that some cations, specially lanthanides, can act as donors or acceptors in RET.

More complicated probes such as retinal can be roughly modeled approximately as a spherocylinder, a cylinder with hemispherical caps on its bases, of $L^* \cong 3$ from the van der Waals radii of atoms in retinal. A spherocylinder can also be seen as a parallel body built at the constant distance σ of the cylinder axis and we may apply our results to this molecule according to usual perturbation theory [24]. Thus, an interpolation in Table I gives a value of $R_0(2/3)/\sigma$ of about 10 for this L^* at low probe densities. Using an approximate value of $\sigma \approx 0.35\,\text{nm}$, this gives $R_0(2/3) \approx 3.5\,\text{nm}$, that is less than the experimental value [25] for R_0 of 4.9 nm. Thus, the isotropic value of κ^2 can be used confidently in this case.

Coming back to our discussion of the present problem, we see that an MD simulation of a free molecule can give us some clear insights into the behavior of a probe in RET. Indeed, the results presented here provide a guide of previous conditions to choose a confident linear probe for RET. Moreover, time correlation functions obtained from molecular dynamics of simple probe models could help to interpret very recent results of energy transfer at nanoscale [26] and we are currently working on this purpose.

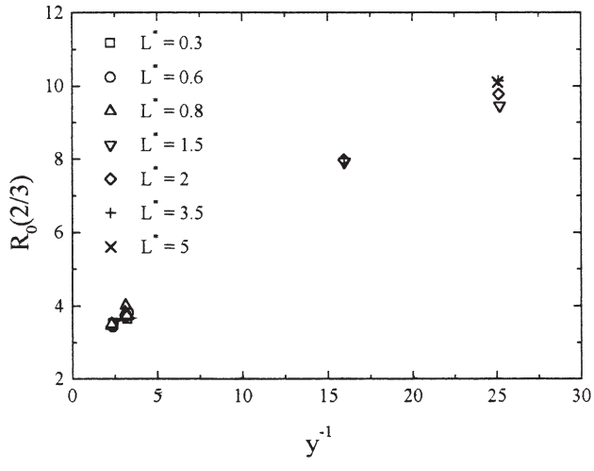

FIGURE 6 Reduced isotropic distance, usually identified with Förster distance versus inverse of packing fraction for the most of systems considered in this work.

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