Entropy driven key-lock assembly

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The effective interaction between a sphere with an open cavity (lock) and a spherical macroparticle (key), both immersed in a hard sphere fluid, is studied by means of Monte Carlo simulations. As a result, a 2d map of the key-lock effective interaction potential is constructed, which leads to the proposal of a self-assembling mechanism: there exists trajectories through which the key-lock pair could assemble avoiding trespassing potential barriers. Hence, solely the entropic contribution can induce their self-assembling even in the absence of attractive forces. This study points out the solvent contribution within the underlying mechanisms of substrate-protein assembly/disassembly processes, which are important steps of the enzyme catalysis and protein mediated transport.

The key-lock (KL) self-assembling mechanism [1] is found in several vital biological processes such as active protein mediated transport [2], enzyme catalysis [3], DNA/RNA transduction and replication [4], among others. It consists on the perfect match of a macromolecule referred to as the key, into an irregular open cavity of another generally larger macromolecule, i.e., the lock. In case of catalysis, the lock particle is an enzyme, which may have more than one cavity to capture different reactants (substrates). The perfect match between the substrates and the enzyme guaranties, at least partially, the specificity of the desired reaction, since the active site (the catalyst active part of the enzyme) is generally situated inside the lock. The specificity is so high that scientists have tried to emulate it for designing their own catalysts [5–7].

In general, the catalytic and protein mediated transport kinetics involve the following steps: assembling, reaction or transport, and disassembling [8]. Since these steps are sequential, a slow step would strongly affect the overall rate of the whole process (bottleneck). Most biological catalytic and protein mediated transport processes are not only specific but also show huge kinetic rates [3, 9], strongly suggesting that the complicated match between the key and the lock and its disassembling do not retard the kinetics of the whole process.

This communication focuses on the collective contribution of the solvent to the effective interaction potential between the key and lock macromolecules, leaving aside the evidently important role of the electrostatic [10], London - van der Waals, hydrogen bonding, end internal KL entropy contributions [11]. Additionally, the considered KL/solvent size ratio and solvent density are still far from a realistic biological system, and so, in this context the results reported here must be considered as a guide only. Since just the exclusion potential energies of the solvent particles and macroparticles are accounted for, the resulting macroparticles interaction force is referred to as entropic [12], depletion [13, 14], or contact [15, 16]. Although solely this interaction is capable of producing phase transitions, clusters growing, and self-assembling processes are sequential, a slow step would strongly affect the overall rate of the whole process (bottleneck). Most biological catalytic and protein mediated transport processes are not only specific but also show huge kinetic rates [3, 9], strongly suggesting that the complicated match between the key and the lock and its disassembling do not retard the kinetics of the whole process.

Previously, the pair potential between hard macroparticles immersed in a hard sphere fluid has been studied [15–23]. In most cases the interaction between convex or planar surfaces has been addressed, and only a few works deal with concave surfaces [14, 21, 24]. In this work we gain insight into the KL self-assembling mechanism by studying the pair potential between a spherical macroparticle with an open spherical cavity (concave surface), the lock, and a hard sphere that fits the cavity, the key, both immersed in a bath of smaller hard sphere particles. To achieve this goal it becomes necessary to analyze the whole 2d energy map from where low energy trajectories can be deduced. These trajectories, which may avoid trespassing potential barriers, are those which would make possible a fast KL self-assembling kinetics. As mentioned, this is a characteristic of the enzymatic catalysis and the protein mediated transport.

Three species are considered: the lock, consisting on a hard sphere of radius $r_l=3\sigma$ having a spherical cavity of radius $r_h$ located at a distance $d = \sqrt{r_l^2 - r_h^2}$ from...
its center; the key, a hard sphere of radius $r_k \leq r_h$; and the solvent, a hard sphere fluid made of particles of diameter $\sigma \leq r_h$. Thus, the KL closest approach distance is $d_{kl} = d - r_h + r_k$. The center of the lock particle is fixed at $(x, y, z) = (0, 0, -d_{kl})$, being the origin of coordinates placed at the center of the simulation box. The position of the key particle is also at the $y = 0$ plane, at a given $(x, z)$ point which varies from run to run. Particles and locations are schematized in Fig. 1a. Unless otherwise indicated, computer experiments were done by setting $r_h = r_k = 1.7\sigma$, so that $d_{kl} = d$. The lengths of the simulation box sides are $L_x = 18\sigma$ and $L_y = 12\sigma$. Solvent particles are initially randomly placed, and then moved according to the Monte Carlo scheme. The bulk solvent volume fraction is set to $\rho_{so} = 0.2$. A snapshot of the system is shown in Fig. 1b.

The contact force acting on a macromolecule is given by $\mathbf{F} = -k_B T \int_A \rho_{sc} ds \mathbf{n}$, where $\rho_{sc}$ is the density profile of the solvent at the macromolecule surface, $\mathbf{n}$ is a unit vector pointing out the surface, $k_B$ is the Boltzmann constant, $T$ is the temperature, and the integral subindex $A$ refers to the macroparticle surface area. $\rho_{sc}$ for the key particle located at $(x, z) = (0.2\sigma, 1.6\sigma)$ is given in Fig. 2 as a function of the angles $\theta$ and $\phi$. These angles are defined as shown in the figure. For the surface region far from the lock, i.e., $\theta > 0.5\pi$, $\rho_{sc}$ is practically constant, $\rho_{sc} \approx 3.4\rho_{so}$ (lighter yellow). Only the region close to the lock surface shows clear variations of $\rho_{sc}$. There is a depletion region (white band at $\theta \approx 0.25\pi$) close to the cavity border of the lock, where solvent particles cannot access. As can be seen, this region (and the whole surface) is $\phi$ dependent since the axial symmetry around $z$ was broken by setting $x \neq 0$. For $\theta \leq 0.2\pi$, $\rho_{sc}$ produces larger values than those for $\theta > 0.5\pi$, since the solvent particles are strongly adsorbed into the lock cavity. Moreover, the largest values of $\rho_{sc} \approx 11.2\rho_{so}$ (darker red) correspond to particles inside the cavity and close to its border. Hence, the region where the cavity and key surfaces are close is preferred by the solvent particles. This suggests that the system is optimizing space by placing solvent particles where a large surface/volume ratio is found. For large $z$, $\rho_{sc}$ tends to be independent of $\theta$ and $\phi$, implying that $\mathbf{F}$ asymptotically decays to zero $\approx \theta$. This long range behavior of the contact force may explain how certain enzymes act on substrates at kinetic rates that approach the encounter rate of the KL in solution.

For the case of Fig. 2, the depletion region does not contribute to counterbalance the force exerted by the solvent on the outer surface of the key, which produces a negative (leftwards/attractive) contribution to the $z$ component of the force, $F_z$. On the other hand, the fringe at $\theta \leq 0.2\pi$ tends to counterbalance (and may even overbalance since $\rho_{sc}$ is large in this region) the leftwards $F_z$ contribution. Thus, in this case the sign of $F_z$ is not evident, whereas $F_y = 0$ by symmetry, and $F_z \neq 0$. Note that the average force on the key particle must be equal (with opposite sign) to that acting on the lock particle. This was verified to guarantee the correctness of the algorithm.

$F_z$ calculated for $x = 0$ is shown in Fig. 3a as a function of $z$ (errors are always smaller than symbols). The $F_z$ which results from substituting the lock particle by a hard sphere of radius $r_l$ is also included, i.e., for the lock particle without the cavity (unsymmetrical hard spheres, UHS). In Figs. 3b and c it is shown $E_0 = \left(-\int_{-\infty}^{\infty} F_z dz\right)_{x=0}$, i.e., the corresponding effective pair potential energy. For both cases $F_z$ is attractive at contact. However, the cavity induces a KL attractive force more than twice larger than that for the UHS. This result is in agreement with the theoretical prediction of Kinoshita et al. [14, 21]. In terms of energy, this turns into a decrease of $\approx 14k_B T$, i.e., a potential well $\approx 7$ times deeper. Hence, if the UHS potential well is capable of segregating large
particles from the solvent, as found in many colloidal systems \[26\], then the KL potential should produce its self-assembling.

Forces can be understood by analyzing the solvent density profiles at the key surface, \(\rho_{sc}\). The insets of Fig. 3a compare the \(\rho_{sc}\) obtained for a UHS pair with those obtained for the KL pair. By symmetry, these panels are independent of \(\phi\). For the panels corresponding to the macroparticles closest approach distances (1 and 2), it is clearly seen that the depletion region becomes much larger for the KL pair (white fringe), explaining the much larger attraction found for it. On the other hand, the other two panels are obtained for \(z=2.6\sigma\) (3), KL pair case, and a surface-surface separation of \(1.4\sigma\), UHS pair (4). For these separation distances the net forces are positive (repulsive), producing potential barriers. It is observed a single fringe of large \(\rho_{sc}\) values for the UHS case, while a double fringe structure appears for the KL pair. This last structure is produced by the solvent particles adsorbed near the cavity border, inside and outside it. In both cases (3 and 4), the fringes overcompensate the outer solvent pressure yielding a net repulsive force. Thus, the double fringe structure leads to a larger repulsive force than the single one (see the higher peak force for the KL pair than for the UHS one in Fig. 3a).

Both pair potentials show energetic barriers (Figs. 3b and c). The KL pair potential peak is at \(z=2.6\sigma\), while for the UHS is at \(z=3.6\sigma\), i.e., for a surface-surface separation distance of \(\approx 1.2\sigma\) (see Fig. 4). Although the peaks are not very high, less than \(k_B T\), they may hinder the self-assembling kinetics. It should be pointed out that the KL potential barrier is almost twice higher than the UHS one. In addition, these barriers enlarge by increasing the solvent density, so that, they may be quite large for denser solvents such as water. Based solely in these results, one could conclude that the self-assembling kinetics for the KL pair is relatively slow (at least slower than the UHS assembly). As we will show, this is not true.

By computing \(E(x, z) = -\int_{-\infty}^{\infty} F_z dz|_x\) along different values of \(x = \text{const}\) trajectories, the pair potential energy for the KL pair as a function of \(x\) and \(z\) can be obtained.

The results were fitted by a 2d-function by means of the Levenberg-Marquardt method. This function is plotted in Fig. 4. As expected \(E(x, z)\) is not radially symmetric. This implies the presence of KL noncentral forces, which translates into opposite torques acting on the key and the lock macroparticles \[12\]. For \(x = 0\) torques disappear and the trajectory along the map corresponds to the squares curve of Fig. 3b.

The most important finding is that the potential barrier disappears for \(z\) trajectories passing at \(|x| \approx 1.3\sigma\). For \(\psi \gtrsim \pi/10\) (see Fig. 1) for the definition of \(\psi\) the barrier reapers and the energy map converges to a radial dependent map as that corresponding to the UHS case for \(\psi \gtrsim \pi/4\) (circle symbols of Figs. 3a and c). This means that the UHS map is equal to that for the KL pair with the cavity pointing backwards.

Low energy trajectories, which do not trespass potential barriers, are those shown as dotted lines (due to the \(z\) axis symmetry these trajectories form a surface of revolution in space). These trajectories avoid trapping solvent particles inside the cavity, which would exert positive pressure on the KL pair, providing them a way to escape. Upon the key particle overcomes the central potential barrier through the sides, it gets in contact with the lock cavity. Then the macroparticles slides on the cavity surface towards the \((x, z) = (0, 0)\) position. Another relatively low energy way towards this position would be trespassing the potential barrier far from the cavity and follow the dotted-dashed line trajectories shown in Fig. 4. As shown by Figs. 3b) and c, the potential barrier for large \(\psi\) is smaller than that for small \(\psi\). Although this way the KL pair still needs to trespass a potential barrier, it is likely to occur since the external surface of the lock is larger than the cavity area.

FIG. 4. Pair potential energy, \(E(x, z)\), for the KL pair. Bluish colors mean attraction and reddish colors mean repulsion. Darker tones denote larger energy values. Dotted and dashed-dotted lines represent low energy trajectories.

FIG. 5. a) \(F_z\) as a function of \(z\) for \(x=0\). Effective pair potential interaction energy, \(E\). c) Closeup of the same energy data. Square symbols represent \(r_0 = r_h = 1.7\sigma\), circles \(r_h = 1.7\sigma\) and \(r_0 = 1.0\sigma\), and triangles \(r_h = 2.4\sigma\) and \(r_k = 1.7\sigma\).
Up to here the results show that a KL perfect match ($r_h = r_k > \sigma$) not only produces a very low pair potential energy at the closest approach distance but also yields low energetic trajectories. These two facts guaranties a fast KL self assembling. Hereinafter, we focus on how an imperfect match changes the KL pair potential. Two other cases are studied; these are: (a) $r_h = 1.7 \sigma$ and $r_k = 1.0 \sigma$, i.e., the key size was decreased and the lock particle is kept as it was, and (b) $r_h = 2.4 \sigma$ and $r_k = 1.7 \sigma$, i.e., keeping the same key the lock cavity is enlarged (see the drawings of Fig. 5). Case (a) may correspond to the decrease of the key after a breakup reaction inside the lock (an enzyme catalyzed reaction), whereas case (b) may model a protein conformation change (for instance, after the transportation of the key). As mentioned above, the sequential mechanism ends up with the key release, so that the catalyst or the transporter can be recovered. A priory this seems unlikely due to the large energy well found for the perfect match case.

Results for cases (a) and (b) are shown as circles and triangles in Fig. 5 respectively, as well as the KL perfect match results (squares). As can be seen, cases (a) and (b) reach pair potential wells which are approximately half deep than the perfect match case. Hence, both situations, a size decrease of the key by following a breakup reaction or the enlargement of the cavity produced by a conformation change of the lock macroparticle favor the key release.

In summary, our results show that the KL self-assembling is favored by the entropic solvent contribution. In addition, low energy KL self assembling trajectories which avoid trespassing energy barriers are obtained, guarantying a fast KL self-assembling kinetics. During the process, a net torque appears acting on both particles and guiding them to the match position. Finally, a lock conformation change (frequently found during catalysis and active transport processes [11]) produces solvent entropic contributions favoring the key release. Thus, the results agree with the fast assembling/dissassembling steps which occur during the protein mediated transport and the enzyme catalysis processes. Finally, we emphasize that works on enzyme and transport kinetics should account for the solvent entropy changes.

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