Molecular Dynamics Simulations of Isomerization Kinetics in Condensed Fluids

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(Received 24 May 2000)

Simulations of different reaction schemes for isomerization kinetics in a condensed fluid mixture between two species with small differences in the pair energies show that one of the species dominates at late reaction times. The isomerization is performed on the basis of the energy of the two states, either by choosing minimum energy or by use of Boltzmann weighted kinetics. Both kinetics are autocatalytic and establish domain decomposition with critical fluctuations, which ensure the symmetry break. The model(s) offers a possible explanation of the origin of biomolecular chirality.

PACS numbers: 68.10.Jy, 02.70.Ns, 11.30.Qc, 87.15.He

This Letter deals with the asymmetry of nature and the origin of biomolecular chirality. Organic materials are built from *L*-amino acids and sugars of *D*-glucose-like molecules. The most popular theory for the origin of this biomolecular chirality is probably the theory which explains the dominance of one of the enantiomer forms above the other as caused by very small differences in the parity-violating weak interactions in quantum electrodynamics [1]. In other models the dominance of one of the molecular conformations is explained by stereospecific autocatalysis (Frank model). Kondepudi *et al.* [2] demonstrated that crystals which precipitated from a supersaturated solution of an inorganic salt were dominated by a single chiral species, but only when the solution was stirred [3]. For recent reviews, see [4] and [5]. Here it will be demonstrated that there is a fundamental bistability in a racemic mixture of *condensed* fluids of particles which are identical with respect to their (pair) interactions between particles of the same species, but which differ a little with respect to their interactions between different types of particles. The systems of particles are simulated by molecular dynamics (MD) and the kinetics are implemented as described in [6].

In a racemic mixture, that is, a mixture of equal numbers of the two isomers, there will be a small difference between the packing effectiveness of species of the same kind compared to the packing of mixtures of the two species. This difference is small in condensed fluids where the two species are miscible, but it will eventually lead to the formation of crystals of pure enantiomers (Pasteur's experiment). The chirality of organic materials is due to asymmetrical centers, typically carbon atoms in the skeleton with four different covalently bound ligands, and the packing effectiveness is obtained by a stereospecific arrangement. But Pasteur's experiment is a universal, generic phenomenon also with respect to dimension [7]. The outcome of the stereospecific packing effectiveness is a thermodynamic gain in (Gibbs-free) energy. Statistical mechanically the packing effectiveness in condensed fluids can be described as a small difference in the (radial) distribution functions [$g_{AB}(r)$ and $g_{AA}(r) = g_{BB}(r)$] between particles of the two species A and B at a distance, r, and a corresponding small difference in the potentials of mean force between two particles. It must be this generic quality that the kinetics models shall describe.

The MD model is constructed to describe this situation. Typically, the systems consist of $N = 40\,000$ Lennard-Jones particles in an equilibrium state with temperature, T, and number density, ρ, which corresponds to a condensed fluid. Before the isomerization kinetics are started, all the particles interact with Lennard-Jones potentials, which for computational reasons are truncated (as usual) at an interparticle distance $r_{ij} = 2.5\sigma$, and the systems are equilibrated at the condensed fluid state $(T, \rho) = (2, 0.8)$ [8]. At the beginning of the kinetics half of the particles is (randomly) labeled A and the other half is labeled B and the range of interactions is changed so that two A particles or two B particles still interact with the same Lennard-Jones (LJ) potential, but an A particle interacts with a B particle through a LJ potential which is truncated at a shorter distance $r_{AB}(\text{cut}) < 2.5\sigma$ (three values of $r_{AB}(\text{cut})$: 2.0σ, 2.25σ, and 2.4σ, respectively, are used in the simulations). These small differences are not nearly enough to perform a phase separation in the condensed mixture without isomerization kinetics, and the two species are miscible in the condensed states at all the investigated state points [9]. But the small difference in the range of the intermolecular potentials will slightly favor the packing of species of the same kind, which show up as small differences in the particle distribution functions.

Three different kinds of kinetics are implemented. In the first model the kinetics are performed at particle collisions. The isomerization is performed when a pair energy, $u_{ij}(r_{ij}(t))$, at a high energy collision between particles i and j, at at time t exceeds the activation energy, E. The kinetics can be described by the reaction scheme

$$A + A \rightleftharpoons A + B \rightleftharpoons B + B\,, \tag{1}$$

where the activation energy, E_{AB}, for which AB collisions may convert A into B or *vice versa* must be smaller than the corresponding activation energy, $E_{AA} = E_{BB}$, allowing a conversion of one of the particles in AA or BB collisions. This inequality

$$E_{AB} < E_{AA} = E_{BB} \tag{2}$$

describes the fact that the stereospecific conformational form of a species in a condensed fluid is better maintained in an environment of the same type of enantiomer molecules. The model is bistable for a sufficient difference between the two activation energies and will result in a dominance of one of the species.

This "collision induced activation model" (CIA), described above, can be further simplified and in the second model the conversion from one type to the other is simply performed as

$$A \rightleftharpoons B \tag{3}$$

whenever the potential energy, $u_i(t)$, of a particle exceeds the activation energy, E. This simple "Arrhenius activation energy" (AE) model is also bistable.

The third model describes the isomerization as an "enzyme activated process" (EA). (In fact, some isomerizations are known to be enzyme activated and to give racemic mixtures, but at low concentrations of the species.) The isomerizations are performed inside small "enzyme" spheres which are randomly distributed in the volume. Whenever a particle diffuses into an enzyme volume a conversion might take place. This model is also bistable. All three kinetic models are bistable when the reactions take place in a condensed fluid and give a total dominance of one of the species, but it is not possible to predict which species will dominate, nor when the dominance appears, even if one starts from the same configuration and uses different models or reaction rates. More than a hundred experiments with different sizes (N), dimensions (2D, 3D), temperatures, densities, differences in pair energies [$r_{AB}(\text{cut}) = 2.0\sigma$, 2.25σ, and 2.4σ], and start configurations gave an equal number of dominance of each species within the statistical accuracy.

The central part in the MD models is the selection rule for the conversions, once an activation criterion is fulfilled. The conversions are performed on the basis of the energy difference between the two states, ΔE: Let particle i at time t be an activated A particle. The total potential energy of the particle, $u_{i,A}(\mathbf{r}^{\mathbf{N}}(t))$ is calculated, as well as $u_{i,B}(\mathbf{r}^{\mathbf{N}}(t))$ if the particle i is a B particle and the difference

$$\Delta E = u_{i,B}(\mathbf{r}^{\mathbf{N}}(t)) - u_{i,A}(\mathbf{r}^{\mathbf{N}}(t)) \tag{4}$$

is used to perform the kinetics.

In a diluted solution of a chiral molecule the two energy conformations must have almost the same energy, but, in concentrated solutions and at high pressure, one expects that the packing effectiveness results in an energy difference ΔE. In most of the simulations the exchanges are simply performed when $\Delta E < 0$ [minimum energy (ME)]. It models a MD excited "molecule" with two equal intramolecular energy states and exposed to an external medium force, given by ΔE. In the excited state at the saddle point even a small external medium force will bring it toward the state with smallest energy. But the intramolecular energy state must be chosen with a Boltzmann probability if one describes the medium effect as a thermodynamic force on the chiral molecule, and in a set of experiments the identity is changed with the normalized Boltzmann probability (BP)

$$p = \frac{e^{-\Delta E/kT}}{1 + e^{-\Delta E/kT}} \tag{5}$$

often used for kinetics in statistical physics [10].

Both exchange criteria are autocatalytic. They favor domains of particles with the same identity and it is this quality that ensures the symmetry break. Figures 1 and 2 demonstrate this fact. The figures show the time evolution of the order parameter

$$\eta \equiv \frac{N_A - N_B}{N_A + N_B} \tag{6}$$

for a 3D system of particles starting from the same configuration, but with different activation energies.

Figure 1 is for a CIA + ME kinetics and Fig. 2 is for the corresponding CIA + BP kinetics. The activation energy E_{AB} is set to $3kT$, which gives a mean rate of reaction of five conversions per time step for 40 000 particles. The time evolutions of $\eta(t)$ are for different values of the activation energy, $E_{AA} = E_{BB} = E_{AB} + nkT$. For $n \leq 1$ the mixture remains in a homogeneous racemic mixture with the order parameter fluctuating with a small amplitude around the mean value $\langle \eta \rangle \approx 0$. For the same start configuration the mixture is bistable for $n \geq 2$ and ends up in a configuration with one of the species as a solvent, (s), and a low and uniform concentration of the remaining outnumbered species, (i), corresponding to the classical kinetics result

$$\langle N_i \rangle = \langle N_s \rangle e^{-(E_{AA}-E_{AB})/kT}. \tag{7}$$

The bistability, however, does not always appear at the beginning and for the experiment, shown in Fig. 1, the

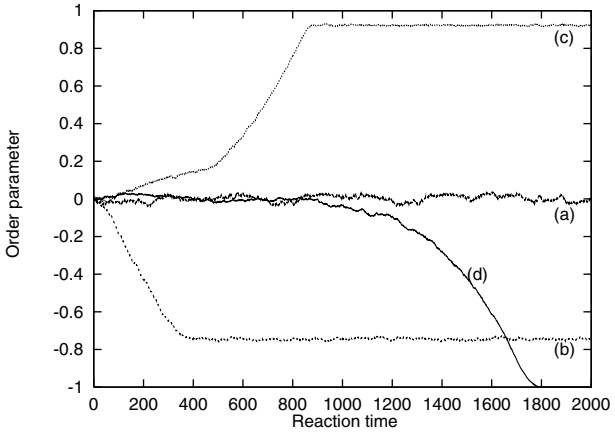

FIG. 1. Order parameter, $\eta = (N_A - N_B)/(N_A + N_B)$, as a function of reaction time and using CIA + ME kinetics. The reactions are all for $r_{AB}(\text{cut}) = 2.0\sigma$ and an activation energy $E_{AB} = 3kT$ and different values of $E_{AA} = E_{BB}$. (a) $E_{AA} = E_{AB} + kT$. (b) $E_{AB} + 2kT$. (c) $E_{AB} + 3kT$. (d) $E_{AA} = E_{BB} = \infty$.

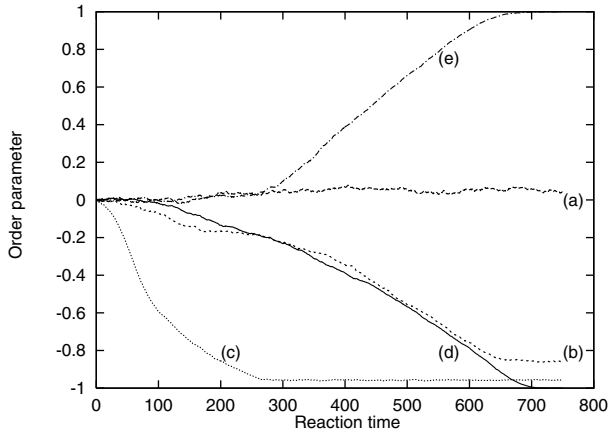

FIG. 2. Order parameter, η, for the same system as shown in Fig. 1, but with a Boltzmann kinetics (CIA + BP) instead of a minimum energy (CIA + ME) kinetics. (a)–(d) are for $r_{AB}(\text{cut}) = 2.0\sigma$, and (e) is for $r_{AB}(\text{cut}) = 2.25\sigma$ and with $E_{AA} = E_{BB} = \infty$. For $r_{AB}(\text{cut}) = 2.40\sigma$ the mixture remains stable with $\langle\eta\rangle \approx 0$.

system with the biggest difference in activation energies, (d), remained with an order parameter fluctuating around zero for a reaction time of $\mathcal{T} \approx 1000$ before the bistability showed up. (This behavior will be explained later.) The bistability is manifested in two to three steps. Within a relatively short time the kinetics build up networks of microclusters of the two species due to the small energy gain by a conversion to a local environment consisting of particles of the same species. This can be seen in Fig. 3(a). The figures show particle distributions of the A particles for a two-dimensional system and for EA + ME kinetics. The first distribution, (a), is after a short reaction time $\mathcal{T} = 50$ (10^4 time steps). Within this time the separation into a diffuse percolating network of both species has already taken place, and the distribution built up by the kinetics reminds one of the early stage of spinodal decomposition in a critical mixture, but without conserved order parameter.

The next distribution, (b), shows the distribution in the second part of the kinetics for the minority species, and in this experiment the A system is going to lose. In this part of the kinetics where there is a coarsening of diffuse subphases, the kinetics mainly take place in the interface zones. A species at an interface that is concave with respect to the same species will not be converted so easily as if its "own species" interface is convex. This is simply due to the reacting particle having fewer nearest neighbors of its own kind when placed at a convex interface than a concave interface. Thus, e.g., a droplet of a species surrounded by a percolating phase of the other species will lose even if the number of particles in the droplet is bigger than the number of the other species, simply due to the curvature of the interface.

The mechanism of the phase growth has something in common with spinodal decomposition since the kinetics will suppress curvature of the interface. In most of the experiments performed for the 3D system the dominance of

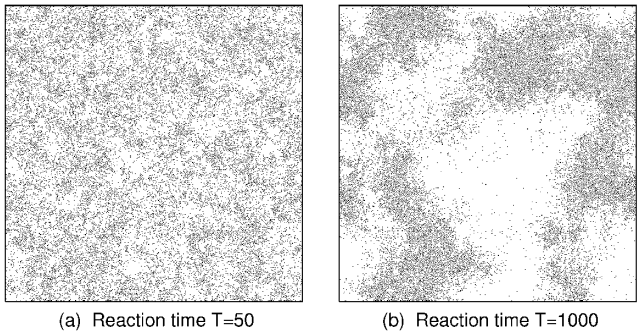

FIG. 3. Particle distributions of the A particles and for the enzyme activated + minimum energy kinetics (EA + ME) with a particle fraction of enzymes of 0.0125. Similar domain structures are obtained for the other kinds of kinetics (CIA and AE and with ME or BP).

one of the species was established already early and the nonpercolating phase lost, as can be seen in Fig. 1 for the kinetics (b) and (c). But in some cases (especially in 2D) both species percolated the volume at early time of the evolution, and then the system can remain with both species in separated phases for a very long time [Fig. 1(d)]. At first it might appear as a mystery why one species after all is going to dominate the other in this case, since any percolating interface must contain convex as well as concave pieces. A picture of the interface between two percolating domains of A and B particles explains, however, the phenomenon: Let this percolating interface be resolved in a sum of (concentration of a species) waves with different wavelengths. The kinetics will suppress all waves since the species will be removed from the convex top of its "home" phase and will be created at the concave bottom. But the kinetics will suppress the curvatures with the smallest wavelength, and for spinodal decompositions this coarsening will result in the final phase separation with equilibrium planar interfaces and with surface riplons with a noncritical power spectrum of frequencies. When this is not going to happen in the case of this kinetics driven separation it is because the interfaces are established by the kinetics and the surface tension, γ, of the interfaces is very small due to the small difference in the potential energy of the two species with subphases of equal densities. This means that the kinetics driven phase separation has a structure with a *biased critical-like* behavior. It is biased because it suppresses the small wavelength fluctuations but leaves the long wavelength fluctuations untouched, and it is critical-like due to the small surface tension. Thus it is only a matter of time, even when the two percolating systems are fully separated, before a sufficiently big fluctuation breaks one of the connections between subdomains in one of the phases and then one of the species will dominate. This is what happens in the kinetics shown in curve (d) in Fig. 1.

This explanation can be verified by starting from particle configurations with separated species in percolating subphases. The surface tension in these 2D and 3D

systems with well defined interfaces can be calculated from the pressure tensor p_N and $p_T(z)$ normal and parallel to the interfaces [11],

$$\gamma = \int [p_N - p_T(z)]\, dz\,. \tag{8}$$

The surface tension in a 3D system and with CIA + ME kinetics is almost zero, $\gamma\sigma/\epsilon < 0.001$ and one of the species dominated after $\mathcal{T} \approx 500$. In 2D the symmetry break appeared after $\mathcal{T} = 71\,000$ (1.43×10^7 time steps).

In summary, the packing effectiveness, due to a stereospecific arrangement of chiral molecules, is described as an intermolecular medium force. The isomerization kinetics in condensed fluids are simulated by use of three different activation mechanisms. The activation to the excited state, where a molecule can perform a (conformational) energy change, is either reached by particle collision induced activation, by a simple Arrhenius activation energy mechanism, or at some enzyme active locations. The "conformational" change is then performed on the basis of the energy difference, ΔE, between the two states. In most of the simulations a conversion is performed if the change, ΔE, to the new state is negative (ME), which simulates the intermolecular medium effect as a simple intermolecular force on the activated molecule. In some simulations the ME criteria are replaced by a Boltzmann weighted exchange probability, which simulates the medium effect as a thermodynamics force. Both criteria are autocatalytic and ensure a symmetry break and a total dominance of one of the two species for all three activation mechanisms.

The model(s) offers a possible explanation of the origin of biomolecular chirality. The gain in (Gibbs-free) energy due to the packing effectiveness in a mixture of chiral molecules must increase with increasing pressure and the symmetry break could have happened under high pressure in a condensed mixture of these molecules. One shall, however, expect that also the activation energy increases with increasing pressure. In order to obtain experimental evidence for the proposed mechanism of the symmetry break it might be necessary also to maintain a high isomerization rate, e.g., by the use of stereoneutral catalysis at solid surfaces.

I thank E. Velasco for many helpful discussions and critical comments.

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