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Monte Carlo simulation of enantioseparation process.

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Abstract

By means of Monte Carlo simulation, a study of enantioseparation by capillary electrophoresis has been carried out. A simplified system consisting of two enantiomers S (R) and a selector chiral C, which reacts with the enantiomers to form complexes RC (SC), have been considered. The dependence of $\Delta\mu$ (enantioseparation) with the concentration of chiral selector and with the temperature have been analyzed by using the simulation. The effect of the binding constant and the charge of the complexes are also analyzed. The results are qualitatively satisfactory, despite the simplicity of the model.

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I. INTRODUCTION

Almost half of the drugs used in therapeutics have at least a chiral center. In most cases the pharmacological activity is restricted to one of the enantiomers; the remaining has either no effect or can produce different therapeutic or even adverse effects [1]. The pharmaceutical analysis including drug quality control, toxicological investigations, pharmacodynamic and pharmacokinetic studies, require the development of enantioselective methods. Separations of enantiomer compounds have been achieved by using several instrumental techniques such as high-performance liquid chromatography (HPLC) [2–4], gas chromatography [5, 6], supercritical and subcritical fluid chromatography [7, 8], capillary electrophoresis (CE) and capillary electrochromatography [9–11]. In CE, chiral separations have been carried out by using chiral additives in the background electrolyte (BGE), in particular cyclodextrins are the most used additives for this purpose [12–16]. In 1992, Wren and Rowe [17, 18] established the theoretical background for enantioseparation by CE using the phenomenological equation introduced by Stepanov and Stepanova in 1969 [19]. According to the model the degree of separation depends on the concentration of the chiral selector, existing an optimum concentration. Two critical points should be mentioned when applying the aforementioned model for optimization purposes in chiral CE: i) The maximal mobility difference between the enantiomers does not a priori mean the maximal resolution; and ii) The model does not cover several major parameters affecting chiral CE separations. However, the model has found wide acceptance due to two main reasons: its relative simplicity and the fact that the chiral selector concentration represents one of the major variables in chiral CE [13]. An important contribution to the understanding of the process was done by Rizzi [20] and Chankvetadze [21].

These theoretical studies generally are based on simple mean-field arguments. However, a detailed study of the process, should consider all possible events or transitions (jumps, reactions, etc.) of each of the particles involved. Experimental studies have not generally been designed to elucidate the mechanisms occurring at the molecular level during enantioseparation process. One of the most appropriate tools to analyze the whole process seems to be the numerical simulation, particularly the Monte Carlo method [22–36].

Monte Carlo simulation appears particularly useful to investigate strongly interacting systems. The calculation of static (or equilibrium) properties has been long investigated and

upgraded in such a way that numerous algorithms are currently available that quickly relax the system from arbitrary initial configurations to equilibrium [23–26]. However, in most cases the local dynamics of the original system is appreciably distorted, such that the kinetic behavior in the non-equilibrium, as well as in the stationary regime, become meaningless (think of a lattice gas where a natural local dynamics driven by jump of adsorbed molecules to nearest neighbor empty sites is replaced by a nonlocal relaxation algorithm allowing the molecule to jump over any empty site of the lattice regardless of its separation from the starting site).

The standard Monte Carlo simulations (SMC) of collective dynamics have been already performed in several processes like surface processes. However, the use of SMC (i.e. Metropolis scheme [27, 28]) under some conditions (temperature far below the critical one, etc.) may turn the simulation of collective dynamics into an exceedingly time-demanding task. In order to overcome such difficulties, one possible solution is to implement the well-known kinetic Monte Carlo simulation [29–34, 37–40].

The objective of this work is the use of a kinetic Monte Carlo simulation to analyze with certain detail, the phenomenon of capillary electrophoresis, particularly as related to the resolution of enantiomers. Despite the simplicity of the model, the most important aspects of the process are taken into account, in order to understand the mechanisms that occur at the molecular level, according as the separation process takes place. The outline of the papers is as follows: in Section 2, the model and the kinetic Monte Carlo scheme is described, in particular the algorithm of simulation. In Section 3, our results are shown and finally, in Section 4, the conclusion is presented.

II. THE MODEL AND THE KINETIC MONTE CARLO SCHEME

In order to simulate the enantioseparation process, an array of $L \times M$ sites forming a two-dimensional lattice with square symmetry is considered to mimic the capillary system. Periodic boundary condition in one direction and free boundary condition in the other, in which the high electrical field is applied is also considered. This represents sites distributed on the surfaces of a cylinder. Initially the sites of the lattice are empty. It is important to emphasize that the sites of the network used for simulating the system represent the position of the particles of the system and are not associated with any kind of intrinsic

energy. On the other hand, it is important to note that in this model, the jump length has been considered constant and equal to the lattice constant, this has no implication on the dynamics of the particle but facilitates the implementation of the simulation. Then, an initial concentration of chiral selector C (usually, β -cyclodextrin), is randomly distributed on the whole system. Then a racemic binary mixture of enantiomer (R and S) is randomly distributed in the higher electrical potential region of the system.

After reaction with the chiral selector (β -cyclodextrin), the complexes present different electrical charges.

The complexation between the R (S) enantiomers and the chiral selector C occurs according to the binding constants K_R (K_S). The reaction scheme is as follows:



and



The equilibrium constant K_{SC} and K_{RC} are related to the Gibbs Free Energies of the complexation reactions, ΔG_{RC} and ΔG_{SC} , according to

$$K_R = \exp(-\Delta G_R/KT) \quad (3)$$

and

$$K_S = \exp(-\Delta G_S/KT). \quad (4)$$

After that, the sites of the lattices can be empty or occupied by a chiral selector molecule C, a transient state molecule, RC^* or SC^* , and after a given time of simulation the definitive complexes molecules, RC or SC are also found. Double occupancy is forbidden. Note that, the transition state is considered by the fact that the reaction is not instantaneous, and both the enantiomer and chiral selector need some time on the same site before reacting. In our model, the chiral selector molecules are supposed to be fixed in the lattice sites. The movement of these molecules decreases the arrival time, but does not affect the enantioseparation process, however this assumption simplifies the simulation model. The

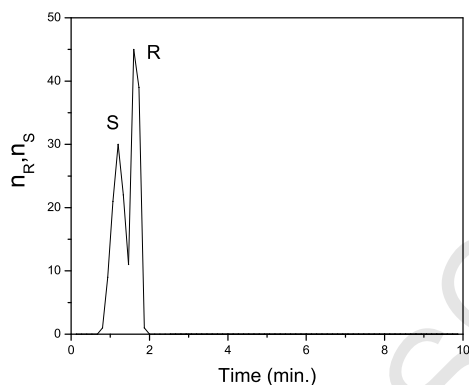


FIG. 1: : Electropherogram obtained by Monte Carlo simulation (the parameters are described in the text).

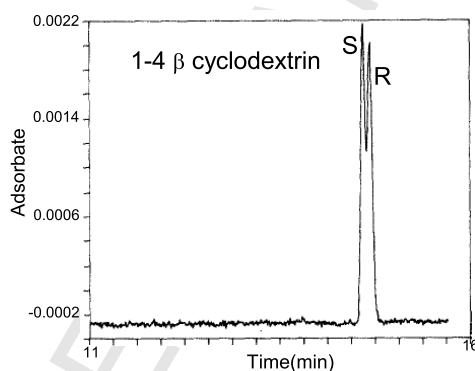


FIG. 2: : Experimental electropherogram obtained in Ref. [17] for propranolol enantiomers at the optimum β -cyclodextrin concentration. As is expected, the time scale corresponding to the simulation and experimental results are not coinciding.

applied electric field determines that the complex, electrically charged, move to regions of lower electrical potential energy, where the detector is located.

Jumps between adjacent sites are only allowed for the charged particles (complexes). The jump activation energy takes into account several factors as follows: *a*) the effect of the electrical field on the complexes; *b*) the friction force between the complexes and the buffer; and *c*) the effect of the flow. The first factor modifies the electrical potential energy of the

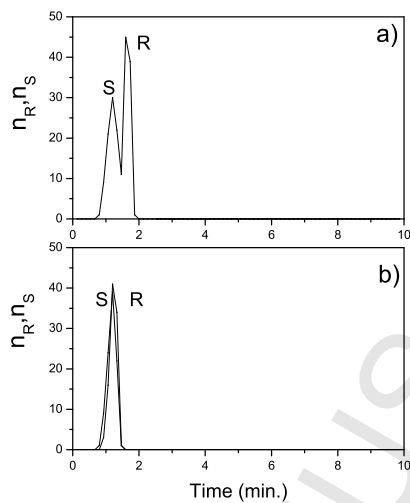


FIG. 3: : Effect on the enantioseparation of: a) difference in the charges of the complexes, b) difference in binding constants.

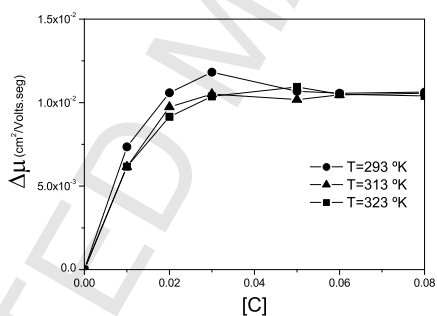


FIG. 4: : Monte Carlo simulation results for the apparent electrophoretic mobility differences as a function of the chiral concentration for different temperatures.

complex,

$$\Delta E_p = q_{RC} \Delta \phi \quad (5)$$

where, ΔE_p , is the change of potential energy to jump from one site to the next, $\Delta \phi$, is the change in electrical potential of the jump, and, q_{RC} , is the charge of the complex (RC). The second factor considers the change in the kinetic energy of the complex due to the work

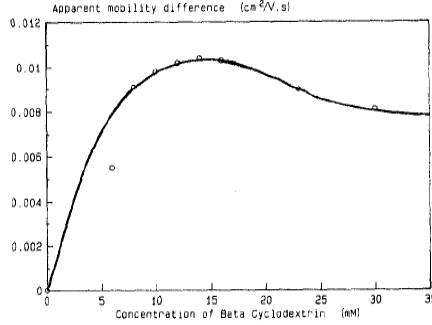


FIG. 5: : Experimental results for the apparent electrophoretic mobility difference as a function of the chiral concentration at $T = 293^{\circ}K$. The symbols correspond to experiment, while the solid line to the Mean Field Solution [17].

done by the friction force when the jump to the next site is done

$$\Delta E_c^{f_r} = \hat{f}_r \cdot \Delta \hat{l} \quad (6)$$

where, \hat{f}_r , is the friction force and, $\Delta \hat{l}$, is the length of the jump (this coincide with the lattice constant). Finally, the third factor refers to the flow effect on the particle given by $\Delta E_c^{f_x}$.

In our model the effect of the friction and the flow affect in the same way to both enantiomers, therefore they do not contribute on the enantioseparation process.

In order to develop a simulation model for describing the enantioseparation process, will be define the elementary transition probabilities per unit time, w_{ij} , from the initial state i to the final state j . The final state j could be the molecule occupying one of the nearest-neighbor (NN) empty site of the system, or the molecule of a given enantiomer after reacting with the chiral selector, etc. Let

$$r_i = \sum_{i \neq j} w_{ij} \quad \text{and} \quad R = \sum_i r_i \quad (7)$$

be the total probabilities for particle at initial state i and for the whole system, respectively, to change its state per unit time. Then, the probability for the system to change its state at a time in the interval $(t, t + dt)$ is given by (Poisson process):

$$P(t)dt = R \exp(-Rt)dt \quad (8)$$

This means that the time elapsed before the system makes a transition should be obtained as

$$dt = -\frac{1}{R} \ln(\zeta) \quad (9)$$

where ζ is a random number uniformly distributed between 0 and 1 [39]. Note that Eq.(9) is applicable even if the system under consideration contains only a few particles. Nevertheless, in the present case, we always shall have a lot of molecules.

The fact that the whole enantioseparation process can be described as a Poisson process is an attractive prospect, since the relationship between Monte Carlo time and real time can be clearly established in terms of the dynamics of individual species comprising the ensemble [33, 34]. On the other hand, a particularly useful feature of the Poisson process is that an ensemble of independent Poisson processes will behave as one, large Poisson process such that statistical properties of the ensemble can be formulated in terms of the dynamics of individual processes.

The transition probabilities w have not been specified yet. However, for thermally activated processes, in particular for jumps from site i to site f the expression is:

$$w_{if} = \nu \exp -(\Delta E/KT) \quad (10)$$

where, K , is the Boltzmann constant, T , the temperature, $\Delta E = \Delta E_p + \Delta E_c$, is the change of the energy in the jump and, where $\Delta E_c = \Delta E_c^{f_r} - \Delta E_c^{f_x}$. The factor ν is a frequency of jump per time unit (in the rest of the paper is consider as a constant). While for reactions, the transition probabilities are respectively given by

$$w_R(\{R + C\} \rightarrow \{RC\}) = K_R \quad (11)$$

and similarly

$$w_S(\{S + C\} \rightarrow \{SC\}) = K_S \quad (12)$$

Then, the simulation algorithm is as follows:

i) A fixed concentration of the chiral selector, C , is randomly distributed on the lattice. Then, a lower concentration of racemic mixture of R and S enantiomers is deposited on the sites occupied by C molecules. These molecules are located in one of the edges where the electrical potential is maximum. On the opposite side is the detector.

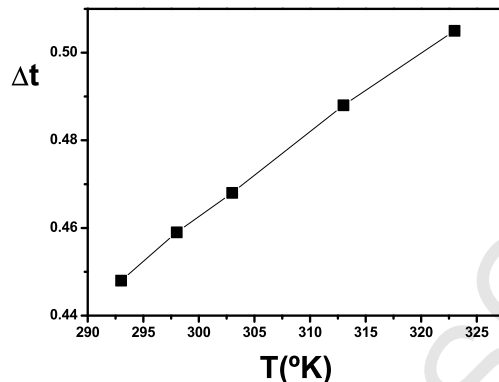


FIG. 6: : Monte Carlo Simulation result for the effect of temperature on enantiomer separation.

ii) A site occupied by RC (SC) or RC*(SC*) is randomly chosen.

iii) If the chosen site is occupied by RC (SC) goes to *v*) otherwise:

iv) A random number ($0 < \xi < 1$) is compared with the normalized probability $P_R = w_R/(w_R + w_S)$, or $P_S = w_S/(w_R + w_S)$ according to the election. If $\xi < P_R(P_S)$ the reaction occurs; otherwise go to *ii*).

v) The normalized probability of jumping to each of the four directions is calculated using Eq.(7) and Eq.(10), in such way that if particles at site *i* can only undergo to one of these final states: 1 jumps to the left; 2, jumps to the right; 3, jumps forward; 4 jumps backward; with probabilities w_{i1} , w_{i2} , w_{i3} and w_{i4} respectively. Then a random number ζ is selected and: if $\zeta < w_{i1}/r_i$, then final state 1 is accepted; if $w_{i1}/r_i < \zeta < (w_{i1} + w_{i2})/r_i$, then final state 2 is accepted; if $(w_{i1} + w_{i2})/r_i < \zeta < (w_{i1} + w_{i2} + w_{i3})/r_i$, the final state 3 is accepted; if $\zeta > (w_{i1} + w_{i2} + w_{i3})/r_i$, the final state 4 is accepted. The particle moves in the chosen direction provided that the site is empty; otherwise, go to *ii*).

vi) This process is repeated until all RC and SC complexes have reached the detector, where they are counted as function of time.

Note that due to the symmetry $w_{i1} = w_{i2}$, the backward and forward jumps are in the direction of the electrical field.

The algorithm is repeated as many times as the number of averages was initially set. In our calculations, the size of the lattices used are $L = 50$ and $M = 500$, while 500 averages were sufficient to obtain a good statistic. The concentration is expressed as the fraction of

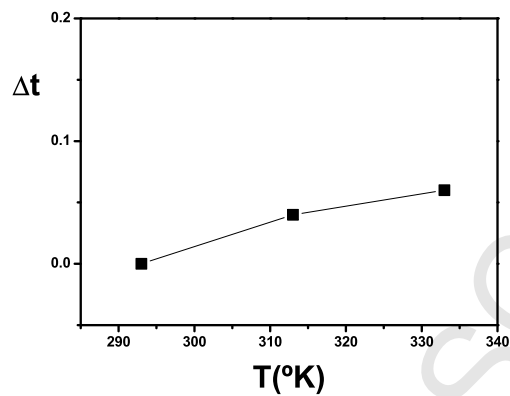


FIG. 7: : Experimental result for the effect of temperature on enantiomer separation [41].

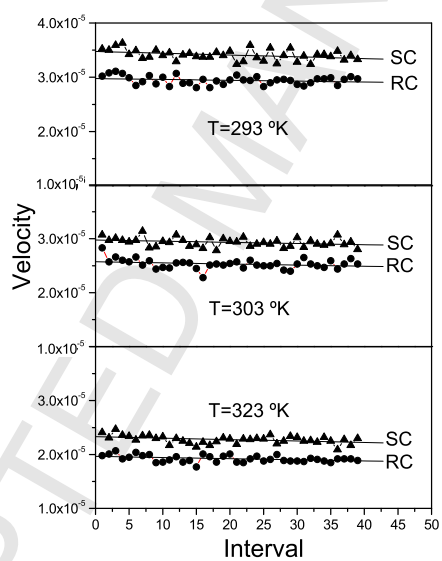


FIG. 8: : Velocity vs time interval. The straight lines are linear fitting of the simulation results.

occupied sites to the total number of sites.

III. RESULTS

In this section, the data obtained by the implementation of the simulation model are presented. A qualitative comparison with some experimental data is shown. A discussion of the results is also given.

To perform the simulations we have defined four parameters: i) the ratio between the electric charges of the complex $\delta = q_{RC}/q_{SC}$; ii) the ratio between the binding constants, defined in eqs.(3) and (4), $\alpha = K_R/K_S$; iii) the loss of kinetic energy of the complexes due to friction with the bulk through $\gamma = \Delta E_c^{f_r}(RC)/\Delta E_c^{f_r}(SC)$; and iv) finally the effect of the flow of ions in the bulk on the rate of the complexes through the ratio $\varphi = \Delta E_c^{f_x}(RC)/\Delta E_c^{f_x}(SC)$. To calculate the enantioseparacion, we assign values to the parameters described above. In the simulation model, the step length, Δl , the electrical potential applied to the ends of the capillary V and the length of the capillary d have taken the following values, $\Delta l = 10\text{\AA}$, $V = 3 \times 10^4$ volts and $d = 0.5$ m, respectively. Note that, both the potential and the length of the capillary are standard values obtained from the device. The complexation free energy used in the present work has been $\Delta G_S = 2.4$ Joule/particles. $\gamma = 1$ and $\varphi = 1$ have been fixed considering that both enantiomers are affected by the friction and the flow in the same way.

Figures 1 and 3 show electropherograms obtained by Monte Carlo simulations. The vertical axis in Fig. 1) and 3), represents the number of particles of the complexes per unit time arriving to the "detector". The concentrations of both enantiomers are $[S] = [R] = 0.02$, while the chiral selector is $[C] = 0.08$ (all the concentrations are measured as the fraction of occupied sites of the lattice). The temperature was fixed at $T = 298^\circ K$. In the Figure 1) the parameters $\alpha = 0.3$ and $\delta = 0.6$ were considered.

In the Figure 2) it is shown an experimental electropherogram obtained in Ref. [17] for (\pm)-propranolol at 14 mM, the optimum β -cyclodextrin concentration. Experimental conditions: buffer phosphate 40 mM, pH 3.12; voltage applied 20 kV; $T=25^\circ C$; hydrodynamic injection 2 seconds; detection at 200 nm. Capillary: I. D. of 75 μm , effective length 50 cm, total length 57 cm.

As is expected, the time scale corresponding to the simulation and experimental results are not coinciding.

The Figure 3 a) shows the effect of the charge difference between the complexes, this is

achieved by maintaining $\alpha = 1$ and $\delta = 0.6$. Figure 3 b) shows the effect of the difference between the binding constants, this is achieved by maintaining $\alpha = 0.3$ and $\delta = 1$ (that means that the charges of both complexes are equal). It is noted that in the simulation model, the effect of the charges produces a larger enantioseparation than the difference between binding constants.

Figure 4) shows the simulation results for the enantioseparation (apparent difference between the electrophoretic mobility), $\Delta\mu$, as a function of the concentration of chiral selector at different temperatures. As a qualitative comparison, the Figure 5) shows $\Delta\mu$ for propranolol enantiomers as a function of β -cyclodextrin concentration at $T = 298^\circ K$. Despite of the difference in the time scale, the same behavior is observed.

Figure 6) shows the effect of temperature on enantiomer separation for a fixed concentration of the chiral selector. The measurement of the enantioseparation is obtained as the difference of the arrival time Δt , of one enantiomer respect of the other. The Monte Carlo Simulation shows that the enantiomer separation has a lineal dependence with temperature (the line is only used as guide for the eye). Similar behavior is observed in Figure 7) where the experimental results, obtained from ref. [41], are shown.

The average velocity of enantiomers was calculated on spatial intervals of equal length along the capillary. As is shown in Figure 8), the average velocity of the SC is higher than the corresponding to RC in whole range. On the other hand, the average velocities decreases as temperature rises.

IV. SUMMARY AND CONCLUSION

In this work we have implemented a model of Monte Carlo simulation to analyze the enantioseparation process. In particular, the influences of the binding constant, the interaction of the charged complexes with the external electrical field and the effect of the temperature on the separation of the racemic enantiomer mixture, have been considered.

The usefulness of the proposed simulation model is based on that, one can analyze, step by step, the effects of different forces at microscopical level, which determine the dynamics of the process.

In the framework of the model presented here, the role of the binding constant in the enantioseparation process is less important than the effect of electrical field in the charged

complexes.

The effect of the temperature is also analyzed, and as main result we observed that as the temperature rises, the difference between the arrivals times to the detector grow linearly with the temperature. On the other hand, the average velocities diminish as temperature rises.

Note that in our simulation the effect of the friction and flow is not taken into account. However, as is observed in the present work, such assumption is confirmed by the simulation results, according with the experimental evidence. Therefore, the contribution of the friction and the flow on the enantioseparation process seems to be not important.

This study, at molecular level, is relevant due that the model reproduces satisfactorily, from qualitative point of view, the experimental results, as the electropherograms and the behavior of the enantioseparation as a function of time, the concentration of [C] [17] and temperature [41]. Despite the simplicity of the simulation model proposed in this paper, we can elucidate some of the molecular mechanisms that could take place in the enantioseparation process.

Acknowledgments

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