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# Brownian dynamics study of the selective orientation of a guest molecule in the surfactant shell of a reverse micelle

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By means of the Brownian dynamics simulation it is shown that the reverse micelle acts as a specific electrostatic template for selective orientation of a guest molecule in the surfactant shell of the micelle; this can be a factor influencing the rate and direction of chemical reactions in the interfacial zone.

Microemulsions are capable of solubilising considerable amounts of water-soluble and oil-soluble substances and a large interfacial area provides proper reaction contact between incompatible species. These properties are responsible for various applications of microemulsions.[1–8]

Microemulsions affect the reaction kinetics due to compartmentalization, concentration or separation of interacting substances.[1–4,9] Particularly, the presence of an oil–water interface may induce the well-defined pre-reaction orientation of reactants, which may affect the regioselectivity of chemical reactions.[2,10,11]

Progress in the use of microemulsions requires a comprehensive analysis of the interaction between the reaction participants and the micellar matrix. We attempted to estimate, by means of the Brownian dynamics (BD) simulation, the orientation of benzoyl-arginine-*p*-nitroanilide (BAPNA) in the hydrophobic domain of the surfactant shell of a reverse micelle under the influence of long-range electrostatic forces and thermal motion. The anionic surfactant, sodium bis(2-ethylhexyl)sulfosuccinate (AOT), obtained a particular recognition in microemulsion route due to its ability to form micelles without a co-surfactant in a broad range of the alteration of water content. A variety of reactions, such as the hydrolysis of ester and peptide bonds, hydration of electron, photoelectron transfer reactions, antibody catalysis, *etc.*, have been studied in the AOT-based reverse micelles.[5,12–15] The choice of BAPNA is conditioned by the non-uniform spatial distribution of the net charge throughout the molecule, its application as a specific substrate for enzyme action in reverse micelles[15] and limited solubility in water.

To our knowledge, this is the first application of the MacroDox programme (version 3.0.0)[16] to the system of two interacting particles when one of them (reverse micelle) constitutes the

supramolecular complex. Initially, the MacroDox programme was processed by Northrup *et al.*,[17,18] and it was successfully applied to study the protein–protein interactions.[19,20]

We consider the system composed of an AOT-based reverse micelle and the molecule of BAPNA. The molecular structures of BAPNA (Figure 1) and AOT were optimised and their charge distributions were determined using a semi-empirical PM3 method. The reverse micelle was composed from 12 AOT molecules with their sulfur atoms placed at the spherical surface with a radius of 7 Å. This system simulates a real small micelle with the water-to-surfactant molar ratio of 4–5.[21] The AOT sulfo groups are taken in dissociated state, the sodium ions being distributed in the inner core of the reverse micelle not far from the AOT polar head groups to make the dipole moment and the total charge of the micelle be equal to zero. The micelle with a settled permittivity of 15 and the BAPNA molecule were placed into a medium with a dielectric permittivity of 2. The micelle is a highly dynamic object, where surfactant molecules strongly fluctuate, both radially and tangentially. However, the possibilities of the applied approach forced us to design the hypothetical micelle rigid somewhat increasing the influence of the steric factor.

The electrostatic field of the micelle can be strongly affected by the level of ionization of the micelle surface under the action of temperature,[22,23] by ionic additives[24] including enzymes and their counter ions,[16,25] thus bringing new properties to the micellar microreactor. To simulate possible alterations in the charge distribution across the micelle under the influence of different factors, we studied the micelles with the total point charge equal to +3e or –3e in addition to the neutral one.

As applied to the concerned model the electrostatic potentials of BAPNA and of the micellar aggregate were determined by a numerical solution of the linearised Poisson–Boltzmann equation in a cubic lattice by the Warwicker–Watson method.[26] The software simulates the motion path of the guest molecule in the electrostatic field of the micelle, which is terminated when the reaction takes place or upon the leaving the potential field of the micelle. The Ermak–McCammon algorithm[27] is used for the trajectory calculation. The coordinates of the particle $i$ are defined according to the following equation:

$$r_i(t+\tau) = r_i(t) + \frac{D_i\tau}{kT}\sum_{j=1}^{N} F_{ij} + R_i(\tau),$$

where $D_i$ is the translational diffusion coefficient of the particle, $F_{ij}$ is the direct interparticle electrostatic force, $R_i(\tau)$ is the random displacement vector used to simulate solvent-mediated Brownian translational motion. The following coefficients calculated by the MacroDox software on the basis of particle size were used: $0.11\times10^{-1}$ and $0.31\times10^{-1}$ Å$^2$ ps$^{-1}$ for the translation motion and $0.23\times10^{-4}$ and $0.45\times10^{-3}$ ps$^{-1}$ for the rotation one for the micelle and the BAPNA molecule, respectively.

The short-range repulsive forces are treated by the prohibition to overlap the exclusion volumes of the atoms. If a BD step leads to the van der Waals overlap, it is repeated until it does not cause the overlap. At the beginning of each trajectory, the BAPNA centre of mass (COM) is placed on a spherical surface with a radius of 50 Å around the COM of micelle. The molecule of BAPNA and the micelle are allowed to rotate and to translate. If the COM of BAPNA reaches the spherical surface with a radius of 200 Å, the trajectory is terminated. After a given number of trajectories, which was usually 20000, the run

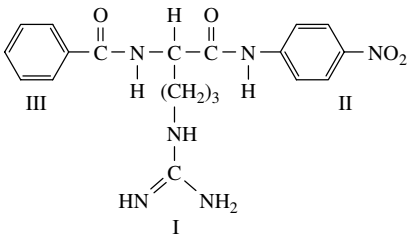


**Figure 1** The contact groups of benzoyl-arginine-*p*-nitroanilide (BAPNA).

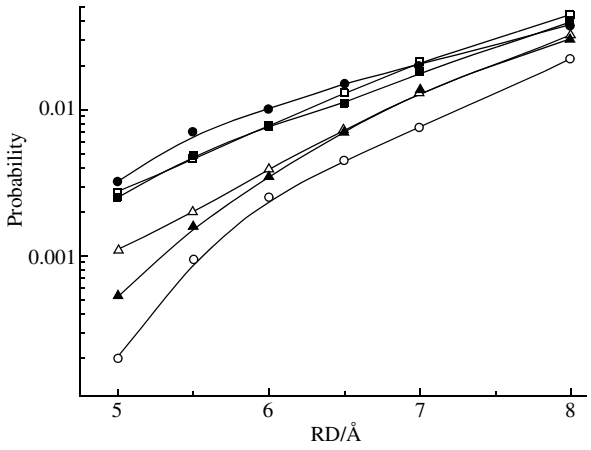


**Figure 2** The probability of EC formation for BAPNA contact groups I (squares), II (circles), III (triangles) for different RD in the presence (closed symbols) and absence (open symbols) of electrostatic interactions between micelles and BAPNA.

was terminated and the relative number of successful trajectories was used to determine the reaction probability. The MacroDox programme declares that a trajectory is successful if two monitored atoms, one of the BAPNA contact groups and any of 12 sulfuric atoms of a micelle come within the 'reaction distance' (RD) one to another and an encounter complex (EC) is formed. The van der Waals radius of heavy atoms is about 1.4–1.7 Å and the RD in the applied approach cannot be shorter than 3 Å (usually, the RD exceeding 6 Å is taken[28]). The shortcomings of BD simulation methods and, particularly, of the MacroDox program were discussed.[20,28] The main disadvantage of the approach is the use of a rigid molecule structure. Slightly irregular distribution of AOT molecules in a micelle should partially overcome this disadvantage. Nevertheless, the influence of the steric factor may be overestimated in our calculations.

Three contact groups were chosen for BAPNA (Figure 1). They are the atoms of the terminal groups: the protons of a guanidinium fragment (I), the oxygens of a nitro group (II) and the *para*- or *meta*-hydrogens of an aromatic ring (III). Although the total charge of the neutral BAPNA molecule is equal to zero, its spatial distribution is not uniform and it is possible to distinguish between the negatively charged nitro group (II) and the positively charged guanidine fragment (I).

Since we consider the micelle as a rigid complex thus bringing steric obstructions for the Brownian motion of a BAPNA molecule, which really are overcome with the help of the internal mobility of micelle, two kinds of calculations have been made to emphasise the influence of electrostatic factors. The first does not take into consideration the electrostatic interaction between the BAPNA molecule and the micelle in contrast to the second one. The results of simulation for all contact groups of the BAPNA molecule are presented in Figure 2. In spite of the zero total charge, the charged micelle behaves as a positively charged system with preferable influence on the negatively charged nitro group (II).

To simulate the influence of possible additives on the alterations in the charge distribution across the micelle, we place a point charge (+3e or –3e) at the micelle centre. The results are presented in Figure 3. The incorporation of the aromatic ring (III) with a nearly neutral charge and the positively charged guanidinium fragment (I) into the micelle shell did not dramatically alter while the heightened sensibility of the negatively charged nitro group (II) to change the orientation is detected.

The results indicate how the micelle can work as a specific electrostatic template, which, under definite conditions, provides a preferable orientation of reagents in the interface with the further, possible influence on chemical reactions in the interfacial zone. Qualitatively, the orientation of a small molecule in the electrostatic field of a micelle and its penetration through the surfactant shell of the micelle do not depend on the choice of a collision criterion.

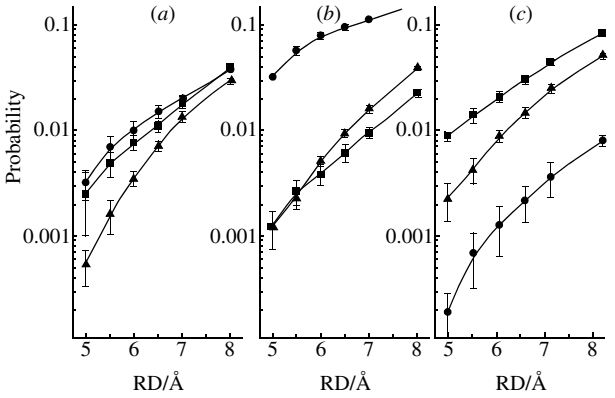


**Figure 3** The probability of EC formation for BAPNA contact groups I (squares), II (circles), III (triangles) for different RD when the total charge of the micelle is equal to (*a*) 0, (*b*) +3e or (*c*) –3e.

Thus, in spite of the simplified model used in this study, we found that the BD simulation allows us to estimate the influence of electrostatic interactions on the selective orientation of an additive/reagent in the surfactant shell of a reverse micelle, which can be useful in the design and analysis of chemical reactions in the interfacial zone.

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