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MONTE CARLO STUDIES OF THE HYDROCARBON REGION OF LIPID BILAYERS

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Summary

We present the results of a Monte Carlo study of systems of hydrocarbon chains attached to a plane interface and interacting through hard core repulsive forces only. The chain-order parameters which we find in our studies are compared to experimental results (NMR and ESR). The role of "kink" states and the relevance of our studies to theoretical models are also discussed.

Introduction

In this paper we report the results of Monte Carlo studies of the physical states of systems of single hydrocarbon chains confined to a monolayer or half a bilayer. Our results provide for the first time a detailed computer description of these systems, which may be compared to both experimental and theoretical results. The state of the hydrocarbon chains in monolayers and bilayers is a timely topic for theoretician and experimentalist alike. At present, ESR measurements with spin labels [1,2] are not consistent with deuterium magnetic resonance measurements [2] of the order parameters. $S_n = \langle 3/2 \cos^2\theta_n - 1/2 \rangle$, where θ_n measures the deviation of the plane of the nth CH_2 group from the plane of the bilayer. In spin labeling experiments S_n decreases continuously as n approaches the terminal end of the chain, in both phospholipid [1] and single chain lipid bilayers [2]. The NMR experiments indicate, however, the S_n remain almost constant in sodium decanoate bilayers until about $n = 7$ and then drops off rapidly [2]. In phospholipid bilayers, the NMR results are similar [3].

The determination of the order parameters S_n is also one goal of theoretical efforts to describe the physical properties of lipid bilayers. To date, the one theory which best agrees with experiment in the calculation of order parameters is that of Marčelja [4]. In this work the final values of the order parameters are determined principally by the attractive forces between CH_2 groups on neighboring chains, in a mean-field approximation. Despite the success of Marčelja's theory, several other workers have attempted to describe the physical state of bilayers by treating the hardcore repulsive force as the principal inter-chain interaction rather than the Van der Waals attractive forces [5—6], while still others have attempted to approximately combine the two interactions into theoretical models [7—9]. Thus, it is desirable from both experimental and theoretical viewpoints to consider the behavior of lipids in bilayers from a third, independent point of view, such as the Monte Carlo analysis we describe here.

Method

The Monte Carlo method used in this work is very similar to that of Curro [10], which successfully simulated the properties of free hydrocarbon chains. We begin with a fixed number of chains. The first carbon in each chain is confined in our model to a plane of specified size, and the remainder of the chains lie below the plane, simulating a monolayer or half bilayer. The remaining carbons in each chain are generated by multiple applications of the rotation operator.

$$\begin{bmatrix} \cos\theta & \sin\theta\cos\phi_i & \sin\theta\sin\phi_i \\ \sin\theta & -\cos\theta\cos\phi_i & -\cos\theta\sin\phi_i \\ 0 & -\sin\phi_i & \cos\phi_i \end{bmatrix} \tag{1}$$

where θ is the angle between successive bonds, set at 70.5°, and ϕ_i is the dihedral or gauche angle for each bond. The allowed values for ϕ_i in the rotational isomeric approximation are 0 and ±120°. An important difference between this work and Curro's Monte Carlo method [10] is that one end of a chain remains attached to an interface and the bond attached to this terminal point has its dihedral angle ϕ fixed at $\phi = 0$. Because the method begins with rotation operations acting on the displacement vector $\left(\begin{smallmatrix}1\\0\\0\end{smallmatrix}\right)$ [10], Matrix 1 will not produce gauche rotations at even numbered bonds in all trans chain segments, since Matrix 1 acting upon $\left(\begin{smallmatrix}1\\0\\0\end{smallmatrix}\right)$ produces a vector independent of ϕ. Also, the method does not produce kinks ($g\pm tg\mp$ sequences), but requires an extra trans segment ($g\pm ttg\mp$). This omission is most likely insignificant for the calculations in ref. 10, because the densities used by Curro are lower by factors of 2—10 than those used here. In the present case, however, corrections must be made in order to simulate systems at greater densities. Otherwise it was found that the model molecules would not pack as closely as they should from simple volumetric considerations. To circumvent this problem, whenever $\left(\begin{smallmatrix}1\\0\\0\end{smallmatrix}\right)$ is encountered, the following matrix for rotations at the next bond is used:

$$\begin{bmatrix} \cos\theta & \sin\theta & 0 \\ \sin\theta\cos\phi & -\cos\theta\cos\phi & -\sin\phi \\ \sin\theta\sin\phi & -\cos\theta\sin\phi & \cos\phi \end{bmatrix} \tag{2}$$

One cannot, however, discard Matrix 1 and use Matrix 2 exclusively, or the same problem described above occurs at odd numbered bonds in all trans segments. Our modification does allow kinks to form along with other molecular conformations which allow for close packing and for this reason it is used in all our simulations. Throughout our computer runs, periodic boundary conditions are imposed in order to simulate more closely large systems.

Each Monte Carlo experiment is begun with the chains uniformly spread throughout the available volume and in the all-trans state. A typical computer run then randomly picks a molecule and translates it as a random distance less than one-half lattice unit (the units are chosen so that the C-C bond length is unity). Then a bond on the same chain is chosen randomly and gauche rotations are considered. A gauche rotation is performed at the randomly chosen bond according to probabilities determined by the assymetrical importance sampling scheme described by Wood [11], and consistent with the rotational-isomeric model. In addition, the chain is rotated through a random angle about the long axis.

At this point the computer checks for overlaps. An overlap occurs if any two carbons come closer than the hard-core radius. The hard-core diameter is taken as 0.95 lattice units. If no overlaps occur, the new state is accepted. If an overlap occurs, the old state is considered to be the new state, and the procedure is repeated. At each step the average chain length and the average order parameter for each carbon atom are calculated and, at selected intervals, the Monte Carlo averages are determined. The order parameters for this model are determined using

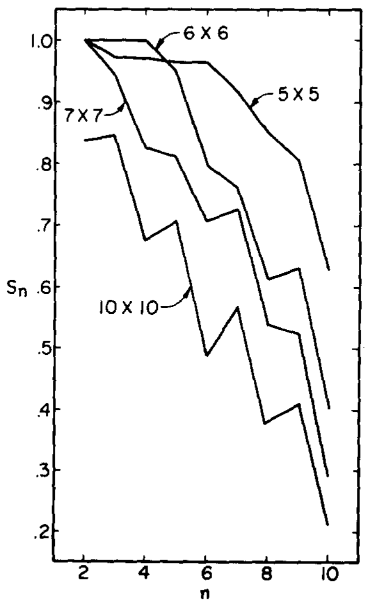
$$S_n = 1/2 \ \langle\langle 3 \cos^2 \theta_n - 1\rangle \qquad (3)$$

where θ_n measures the angular deviation of bond number n from its orientation with respect to the chain axis in the all trans state. The calculations were mostly performed on an IBM 370/158 computer. The random number generator used was the program RANF, written by J.P. Chandler, Computer Science Department, Oklahoma State University. As a check (and for economic reasons), several runs were made on PDP-11 minicomputer, using the random number generator supplied with the machine. A run of 60 000 steps took about 0.5 h on the 370 computer and about 100 h on the minicomputer. Programs are available from the author.

Results

The results of our computer simulations are shown in Figs. 1 and 2. Fig. 1 is a plot of order parameter vs. bond number for systems of 10 chains, 10 bonds long confined to arrays of several sizes. Fig. 2 represents a similar plot for systems of 8 chains, 15 bonds long. All runs in these figures were made using 300 K as the temperature, which plays a role in determining the rotation probabilities. Fig. 3 shows the convergence rate for one of the computer runs of Fig. 1. In Fig. 4 we exhibit the effects of the temperature in our model, by comparing two calculations at 300 K and 400 K for otherwise identical systems.

The errors in the results are estimated by comparing results obtained on the minicomputer with those obtained on the IBM 370/158 for identical configu-



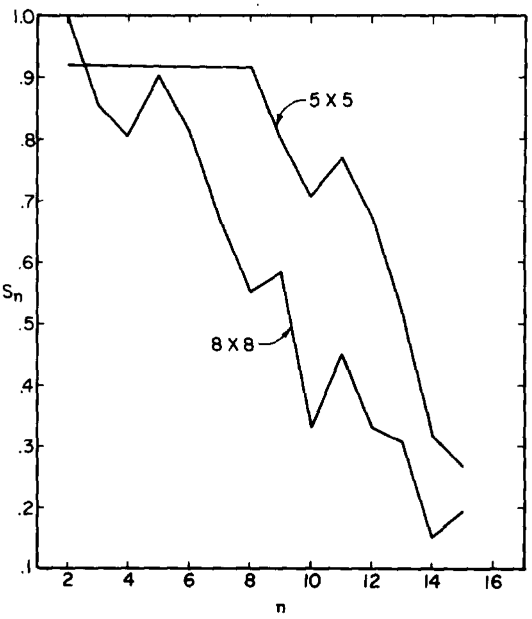
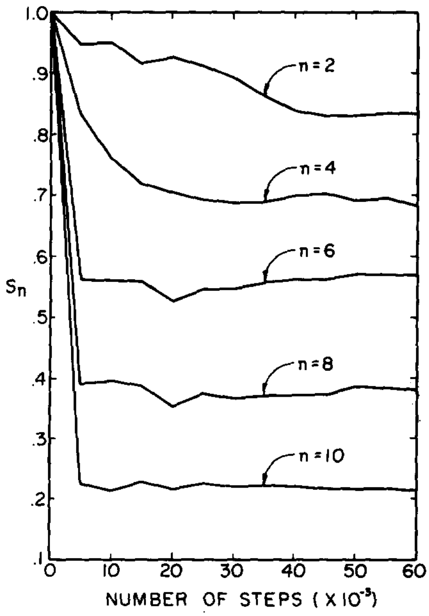


Fig. 1. A plot of S_n vs. n for systems of 10 chains, each containing 10 bonds, confined to arrays of varying size as shown. All runs are 60 000 steps.

Fig. 2. A plot of S_n vs. n for systems of 8 chains, each containing 15 bonds, confined to 8 X 8 and 5 X 5 arrays. All runs are 60 000 steps.



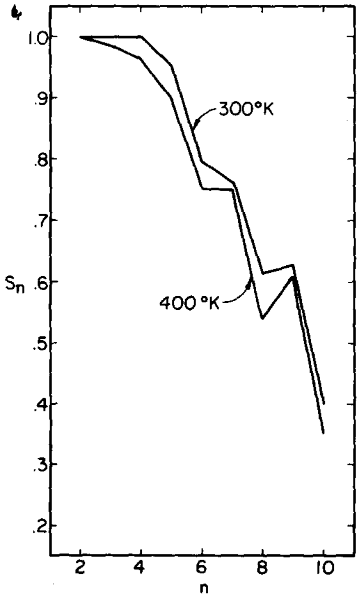


Fig. 3. A plot of the convergence rate for the 10 chain, 10 bond/chain, system confined to a 10 X 10 array. For more tightly packed and/or larger chains more small oscillations occur. Also, long-period oscillatory behavior cannot be ruled out.

Fig. 4. Plots of S_n vs. n for a 10 chain, 10 bond/chain system at T = 300 K and T = 400 K. The temperature enters into these simulations through Boltzmann factors in the Monte Carlo transition probabilities.

rations but using different random number generators. It was found that the differences in S_n tended to be small in the immobile portions of the chains (those for which $S_n \approx 1$) and near the terminal ends, with the largest fluctuations in the intermediate region. Relative differences were less than 15% for all cases for which dual runs were performed. In some cases these differences could be attributed to "out of phase" oscillations in the order parameters. That is, in the different runs order parameters tended to oscillate at approximately the same values, but with different frequencies. In all cases the overall shape of the S_n vs. n plots did not vary significantly.

Discussion

The system modeled in this work consists of a set of chains of spheres with radii approximately equal to the inter-sphere bond length. Computer limitations allow simulation of only a small number of chains confined to a finite volume, interacting only via hard core repulsive forces. Although there are important differences between this system and the alkyl chains in a monolayer or half a bilayer, the results of Curro [10,12] suggest that the present Monte Carlo studies may accurately indicate some aspects of hydrocarbon chain properties.

Figs. 1 and 2 show how the order parameters change as the chain density changes. In overall shape the curves resemble the plots obtained from deuterium NMR experiments [2,3] when the chains are closely packed. They resemble the plots obtained from spin labeling experiments [1] when the chains are loosely packed. These results suggest that when the area per mol is large, the order parameters decrease more rapidly with the carbon atom number than when chains are relatively closely packed. In this latter case the order parameters stay larger until near the terminal carbons, which may have small order parameters. This is consistent with the criticism [2] of spin labels as perturbants to the bilayer structure. If the introduction of spin labels increases, at least locally, the effective area per mol in a bilayer, then the observed difference between NMR and ESR measurements of order parameters is not, in light of our computer simulations, surprising.

Recently, Petersen and Chan [15] have also analyzed the results of the magnetic resonance experiments. They suggest that, under certain conditions, one may separate contributions to the chain-order parameters into two multiplicative components; one due to trans-gauche isomerization and one due to reorientation of entire chains with respect to the bilayer normal. That is, they write order parameters in the form

$$S = S_\beta S_\gamma \qquad (4)$$

where S_β is the contribution due to isomeric disorder and S_γ is due to tilting motions of entire chains. Using a simple model they conclude $0.3 < S_\gamma < 0.58$. Since the present program only considers isomeric disorder in nontilted chains, and for the purpose of comparison of our results with this hypothesis and with the deuterium magnetic resonance data, in Fig. 5 the order parameters obtained in one of the runs of Fig. 1 are plotted along with the DMR data of ref. 2. The computer data are plotted in original form (upper curve) and scaled by a factor

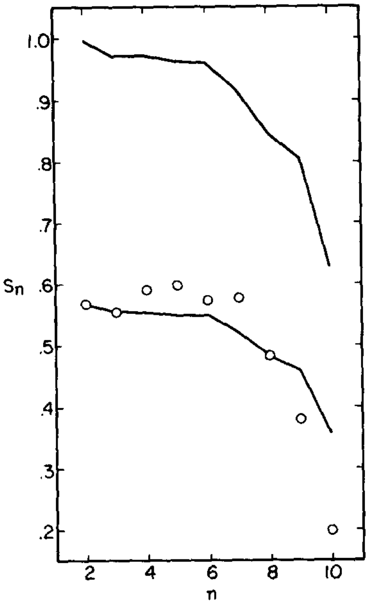


Fig. 5. Upper curve, a plot of S_n vs. n for the 10 chain, 10 bond/chain system in a 5 X 5 array; lower curve, same system as upper curve, but scaled by a factor of 0.57; circles, deuterium NMR data for ref. 2.

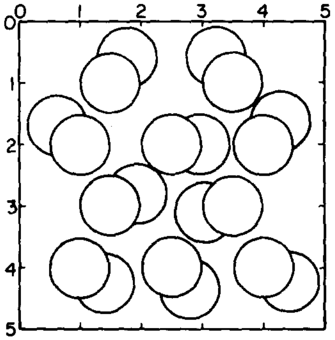


Fig. 6. Diagram of chain packing for 10 chains in a 5 X 5 array, illustrating the portion of available space filled by the chains.

0.57 (lower curve). It is evident that the scaled computer data show fairly good agreement with the experimental points, although the shape of the unscaled curve actually resembles the experimental plot more closely than does the scaled curve.

For closely packed chain systems (5 X 5 and smaller arrays) we found relatively little disorder in the computer runs. The amount of area taken by chains in a 5 X 5 array is shown in Fig. 6. For systems packed more tightly than this, disorder must apparently occur through kink formation [13]. For very tightly packed configurations, the kink formation would require co-operative motions of neighboring chains. Neither of these effects were considered in the simulations. However, in the runs depicted in Fig. 5 the chains had enough freedom to allow kinks to appear spontaneously. When kinks appeared they seemed to be quite stable. Allowing for co-operative (single-step) kink formation and/or simulating the mobility of a kink up and down a chain would have lowered the values we obtained for our order parameters. Nonetheless, the present technique was able, for arrays of approx. 5 X 5 and larger, to produce a very wide variety of isomeric states for the chains and thus we are confident that the results at least qualitatively mirror the true steric behavior of alkyl chain system.

Examination of Fig. 4 shows that, at fixed area, increased temperature does not sharply affect the disorder in the chains. As Figs. 1 and 2 reveal, however, increased area at fixed temperature leads to large scale changes in the disorder. In real systems, of course, increases in temperature lead to increased thermal motion and lateral pressure, which may produce increases in the area per mol. However, as long as the hydrocarbon pressure is balanced by pressure due to hydrophobic forces in bilayers (so that molecular area does not change), little change in chain ordering occurs as temperature changes. This is consistent with the behavior of these systems below the phase transition temperature and is in good agreement with the data of Mely et al. [14].

Two basic differences between the simulated system and actual alkyl chains in bilayers may contribute to the differences between the computer data and the experimental points in Fig. 5. Firstly, the use of spherical molecules with radius equal to the bond length does not correspond to actual alkyl chains. However, by compressing the computer systems to smaller densities until densities such as shown in Fig. 6 are reached, the packing of real alkyl chains is simulated. Thus, this difference is one of scale, and it is expected that the nonspherical shapes of actual CH_2 molecules should not significantly alter one's conclusions. A second basic difference is the size of the system. It is impossible to estimate how much the data would change if the calculations could be performed for, say, 100 chains. The success of Curro's calculations [12] for hydrocarbon liquids, using fewer chains than are used here, suggests that finite size effects are not a serious problem.

The results of the calculations are now considered in the light of the various theoretical models. The computer simulations described here were performed on systems of hydrocarbon chains attached to an interface and interacting only via hard core repulsive forces. These forces alone led to order parameter vs. carbon No. plots which are consistent with known experimental results. This result supports the hypothesis, first framed in a theoretical model by Nagle [5], that the hard-core forces are the most important for chains in bilayers or closely packed monolayers. The Van der Waals attractive forces provide, of course, the attractive energy without which there would be no phase transition. However, it appears that the values of the chain-order parameters are mainly determined by the hard-core forces.

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