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NAVAL RESEARCH LAB WASHINGTON DC B P GABER 01 MAR 87

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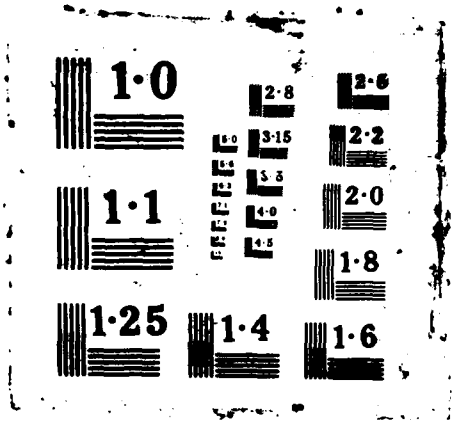
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Molecular Modeling has been applied to three research areas concerned with biomembrane structure: 1) the interaction of stabilizing sugars with phospholipid bilayers; 2) conformational analysis of lipids, and; 3) molecular dynamics of the lipid bilayer.



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Annual Progress Report for Contract #N0001486WR24244
"Molecular Modeling of Lipid Structure and Function"

## PROGRESS

During the past year significant progress has been made toward our major goals of: 1) describing the structure and function of lipid molecules in terms of their interaction with stabilizing disaccharides; 2) defining the stable conformations of lipids and; 3) developing a basis for molecular dynamics studies of lipid bilayers.

Disaccharide Stabilization of the Bilayer: A variety of biological organisms are capable of withstanding extreme dehydration, at which point they enter a phase of dormancy. Upon rehydration these organisms (eg. seeds,yeast) regain full biological activity. The most widely studied anhydrobiotic protectants are the disaccharides (particularly trehalose) which are thought to protect the bilayer by substituting for the stabilizing effect of water.

Anhydrobiotic mechanisms, while interesting in their own right from the standpoint of bilayer/molecule interactions, also provide a critical insight as to how membranes, both natural and artificial, can be protected and preserved under conditions of dehydration. The applications of this information range from stabilization of liposome encapsulated hemoglobin by lyophilization to preservation of isolated tissue.

In the ONR-supported work conducted at NRL, we have begun with a computer graphics model of a bilayer of dimyristoyl phosphatidylcholine (DMPC) which we developed from existing crystallographic data. Building upon this base, we have completed a graphic model which provides a description of the possible mode of interaction of trehalose with the bilayer. The models for the two sugars are very similar, each utilizing three hydrogen bonds to link adjacent type A and Type B DMPC molecules (figure 1). Additional stability results from an hydrophobic interaction between one sugar pyranose ring and an underlying choline residue from a type A DMPC. Sucrose readily conforms to the model as initially developed for trehalose, consistent with the observation of Strauss, et al.[1]

The trehalose interactive model has been subjected to energy minimization using the program AMBER with the result that an additional (bifurcated) hydrogen bond is incorporated into the model. The original hydrogen bonds and the hydrophobic interaction remain unchanged, but the conformation of one pyranose ring converts from chair to twisted boat. This seemingly high energy conformation appears to have resulted from an unfavorably close contact generated in the interactive model, which AMBER attempts to remove regardless of the resulting energetic cost. This possibility is currently being tested by submitting slightly modified interactive models for minimization. Another possibility exists which is that the energetic path to the twisted boat is not as unfavorable as it might seem initially. To explore this possibility, Dr. Barbara Rudolph has systematically examined the potential energy of the

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[1] Strauss, G., Schurtenberger, P., and Hauser, H. Biochim Biophys Acta (1986) 858, 169-180

glucose molecule over a large region of conformation space. The results of these calculations are now being analyzed.

Conformational Analysis of Lipids: Despite years of study on the physical biochemistry of phospholipids, very little is known about the conformational preferences of these molecules. Indeed Sundaralingam published a pioneering study[2] fourteen years ago in which he presented the groundwork for a conformational study of lipids and proposed a system of nomenclature for lipid conformation. A rigorous and systematic of conformational analysis of lipid structures is obligatory for the development of biotechnological applications of lipids and for an understanding of the microstructures which these molecules form in solution.

Such a study has begun. Working with Professor Sasisekharan of the Molecular Biophysics Unit of the Indian Institute of Science during his recent stay at NRL, we have determined that the conformation around the headgroup of a phospho- or sphingolipid may be systematically described with reference to the three torsion angles (alpha, beta, gamma) about the bonds extending from the central carbon atom of glycerol. From this work a generalization of the Sundaralingam torsional notation has been developed and will be proposed in a forthcoming paper. A systematic examination of phosphatidylcholine conformation was begun under Professor Sasisekharan's guidance. The process of analysis involved an initial manual screening of available conformations in order to eliminate those which were obviously unfavorable. The remaining conformations were submitted for energy analysis using AMBER. Table I shows one such set of energy analyses.

Molecular Dynamics: Working in collaboration with members of NRL's Laboratory for Computational Physics (LCP), we have begun the development of a novel approach to the molecular dynamics study of the phospholipid bilayer. Progress in this area has been sufficiently promising that a separate proposal has been submitted in molecular dynamics.

Two major problems confront any molecular dynamics calculation. The first is the determination nearest neighbors. Algorithms exist for this calculation, but they tend to be very expensive in terms of machine time. The second computational problem arises from the need to lengthen the time scale in which the modeling is conducted. A considerable saving can be achieved by constraining molecular bond lengths and angles to fixed values. Existing constraint algorithms, while exact, are slow. Alternative approaches to both of these problems have been developed. They consist of two algorithms: the Monotonic Logical Grid (MLG)[3] and the Multiple Constraint Relaxation (MCR) developed by Drs. Lambarkos and Nagumo and Ms Chandrasekhar.

The MLG/MCR algorithms are being adapted to molecular dynamics by the incorporation of the appropriate molecular force fields. In preliminary tests, we have established a lipid bilayer model consisting of 288 molecules of "united atom" decanoic acid arranged in juxtaposed layers of 12 by 12 molecules. The carboxyl residues are represented by a single atom with an infinite mass as an

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[2] Sundaralingam, M., Ann N.Y. Acad Sci (1972), 195, 324-355

[3] Boris, J., (1986) J. Comput Phys, 66, 1

arbitrary way to maintain bilayer structure. Constraints are established between every third atom. Decanoic acid was chosen for the initial model to be consistent with the molecular dynamics work of Berendsen[4,5]

The initial calculations have been designed to test the stability of the MLG/MCR approach. At the start of a calculation the lipid chains are in the all-**trans** conformation and the chains parallel to the bilayer normal. The only potential present is a Lennard-Jones 6-12 acting on all atoms. The model is then permitted to relax 1 femtosecond per step. At first the kinetic energy increases at the expense of the potential energy. The total energy is conserved. The three components of momentum are conserved, and the magnitude and number of constrained distances that deviate from the constraint value are small. Shortly beyond 8000 time steps "equilibrium" is achieved. That is, the total kinetic and potential energies are seen to fluctuate about some steady value. The calculation of 5000 time steps required approximately 50 minutes of Cray time.

The significance of these initial experiments is that the combination of two novel algorithms (MLG and MCR) for molecular dynamics calculations of lipids produces a result which is physically reasonable and thereby amenable to further refinement and testing. We expect a significant savings in computation time which will translate into the ability to examine dynamic processes in the bilayer on a longer time scale.



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[4] Edholm, O., Berensden, H.J.C., and Van der Ploeg, P. (1983) **Mol Phys**, 48, 379-388

[5] Van der Ploeg, P. and Berendsen, H.J.C. (1983) **Mol Phys**, 49, 233-248

RESEARCH PLANS FOR FY87

Disaccharide Stabilization of the Bilayer: Five additional sugars will be subjected to interactive graphic modeling as described above for trehalose. The initial objective is to test the generality of the model proposed for trehalose. It is expected, for example, that glycerol and inositol will not be accommodated to the model since experimentally they offer no protection against membrane dehydration. The geometries of each of the model bilayer-sugar complexes will be refined by energy minimization procedures using AMBER.

In order to test the validity of the model it is assumed that the sugar-bilayer complex of lowest potential energy provides the greatest degree of stabilization towards dehydration. Thus the computationally-derived minimum potential energy for each of the complexes will be compared to the experimentally-derived stabilizing ability of each carbohydrate.

Conformational Analysis of Lipids: We plan to extend our program of conformational analysis to include phosphatidylserine, phosphatidylethanolamine, and sphingomyelin, in addition to phosphatidylcholine,. The objective is to generate plots in a three coordinate space which will depict the domains of conformational stability for lipids in a manner analogous to the phi-psi maps for peptide conformation. Using the energy analysis and minimization module of AMBER, we will systematically determine the energy of the conformations described by sets of alpha, beta and gamma. Once the intramolecular energies have been described, the intermolecular interactions responsible for self assembly may be investigated in detail.

Molecular Dynamics: Separate ONR funding has been sought for this work, since it is, at this stage, conceptually independent and extremely promising in its own right. We expect the lipid conformational analysis to provide the starting geometries for a later realistic bilayer simulation.

Publications

Gaber, B.P., Chandrasekhar, I. and Pattabiraman, N., "The Interaction of Trehalose with the Phospholipid Bilayer: A Molecular Modeling Study", in **Membranes, Metabolism and Dry Organisms**, A.C. Leopold, ed., Comstock Publishing Associates, Ithaca (1986).

Lambrakos, S., Nagumo, M., Boris, J., Oran, E. and Gaber, B.P., "Molecular Dynamics of A Lipid Bilayer Using Novel Monotonic Logical Grid (MLG) and Multiple Constraint Relaxation (MCR) Algorithms" Biophys J. **51**, 440a (1987) (abstract)

Manuscripts in Preparation

Gaber, B.P., Chandrasekhar, I. "Molecular Modeling of Lipid Structures I. The Interaction of Trehalose and Sucrose with the Phospholipid Bilayer" to be submitted to **Journal of Biomolecular Stereodynamics**.

Nagumo, M., Chandrasekhar, I., Sasisekharan, R., and Gaber, B.P., "Molecular Modeling of Lipid Structure II. "A Systematic Study of the Stable Conformations of Phosphatidylcholine" to be submitted to **Journal of Biomolecular Stereodynamics.**

Gaber, B.P. and Rosenbloom, L, "Molecular Modeling", to be submitted to **IEEE Computer Graphics and Applications.**

Gaber, B.P. and Brown, R., "**Spock**: A Versatile Graphics Package for the Display of Lipid Molecules", to be submitted to **Journal of Molecular Graphics.**

## Table I Caption

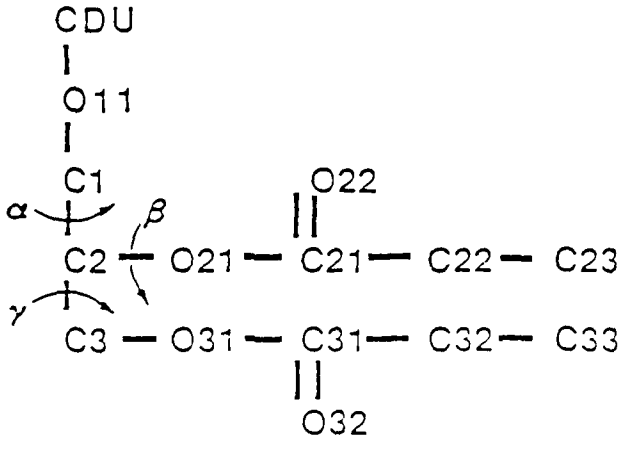
Energies of the principal conformations of the glycerolipid headgroup in kcal $mol^{-1}$, calculated by AMBER. Contributions from the various interactions are listed. Conformations are denoted as follows: $\alpha\beta\gamma$ , where

$\alpha$ = O11-C1-C2-C3
$\beta$ = C1-C2-O21-C21
$\gamma$ = C1-C2-C3-O31

and

G = 60°, "gauche plus"
G_ = 300°, "gauche minus"
T = 180°, "trans"
A = 90°
B = 150°

with the standard dihedral angle sign convention.




model glycerolipid headgroup

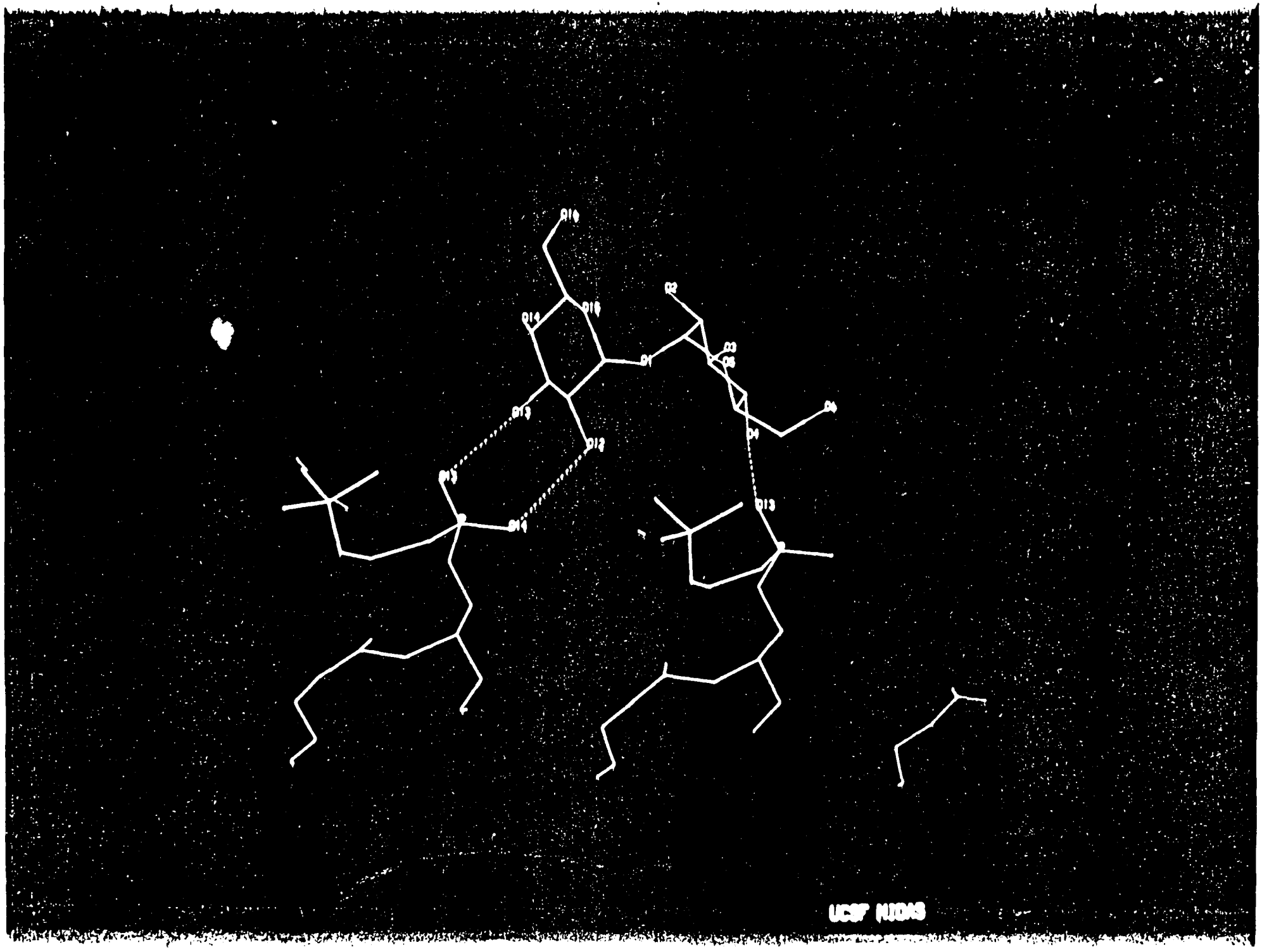
TABLE I

ENERGY

| CONFORMATION | Total | Non Bonded | | | | Bond | Angle | Dihedral |
|---|---|---|---|---|---|---|---|---|
| | | VDW | 1,4 VDW | EL | 1,4 EL | | | |
| GGA | 4.975 | -2.014 | 3.57 | -5.422 | 1.721 | 4.05 | 1.625 | 1.444 |
| GTA | 4.405 | -1.823 | 3.11 | -5.087 | 1.946 | 4.02 | 1.674 | 1.444 |
| GG-A | 7.909 | .368 | 3.402 | -4.176 | 1.222 | 4.06 | 1.673 | 1.444 |
| TGA | 5.569 | -1.137 | 3.229 | -6.078 | 2.443 | 3.98 | 1.681 | 1.442 |
| TTA | 5.166 | -1.102 | 2.829 | -6.389 | 2.669 | 4.03 | 1.679 | 1.442 |
| TG-A | 6.343 | -.978 | 3.121 | -5.365 | 1.945 | 4.50 | 1.677 | 1.442 |
| G-GA | 7.26 | .094 | 3.628 | -5.532 | 2.216 | 4.09 | 1.816 | 1.444 |
| G-TA | 4.31 | -1.99 | 3.222 | -6.572 | 2.443 | 4.08 | 1.681 | 1.444 |
| G-G-A | 4.908 | -2.011 | 3.575 | -5.476 | 1.719 | 4.06 | 1.679 | 1.444 |

## Figure Caption

1. Graphic representation of the interaction of the disaccharide trehalose with a bilayer of dimyristoylphosphatidylcholine (DMPC).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