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**CONFORMATION ANALYSIS OF TREHALOSE.  
MOLECULAR DYNAMICS SIMULATION AND MOLECULAR MECHANICS**

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**Abstract**

**Conformational analysis of the disaccharide trehalose is done by molecular dynamics and molecular mechanics. In spite of the different force fields used in each case, comparison between the molecular dynamics trajectories of the torsional angles of glycosidic linkage and energy conformational map shows a good agreement between both methods. By molecular dynamics it is observed a moderate mobility of the glycosidic linkage. The demands of computer time is comparable in both cases.**

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## 1 Introduction

Conformation of oligo and polysaccharides, besides the particular conformation of the monomers, is characterized by the torsional angles of glycosidic linkage. For most disaccharides two dihedral angles characterise the rotation of the residues around their bonds to the oxygen of the glycosidic linkage. The conformation corresponding to the global energy minimum, as well conformational maps are the usual output from molecular mechanics. If such maps contain enough data, covering most of the  $\Phi$ ,  $\Psi$  plane, it is possible infer the most probable conformation. For favorable cases of multiple minimum maps for which their free energy can be estimated, it may be also available the equilibrium distribution of states and the interconversion rates between conformers [1]. Molecular dynamics, on the other hand, gives the information as temporal trajectories and, if the time span of simulation is enough, allows to obtain the life time of each possible conformation. In both cases one may expect that the results are sensitive to the force field used. This is partially true and there are aspects that are much insensitive to changes in the interaction potential. For instance, the location of minima in molecular mechanics are almost independent of force field, while the interconversion rates are drastically affected. Other aspect to be carefully considered is the use of torsion potentials that may favor some particular conformation.

In the present paper we have considered the conformation of the trehalose ( $\alpha$ -D-glucopyranosil-(1-1)- $\alpha$ -D-glucopyranose) by molecular dynamic simulation (MD), mass weighted molecular mechanics (MWMD) [2], and molecular mechanics (MM). The selection of trehalose is based on its important properties as life-protector in water stress. It is considered as responsible of survival of the so-called *resurrection plants* as well of some highly resistant insects to dryness. It has also properties as a *cryo-protector*.

The results agree well between the two method studied, although the ratio between computer cost and information favored the molecular dynamics studies.

## 2 Methods

Molecular dynamics simulation was performed by using the GROMOS package (Biosmos n.v., Groningen-Zurich) running in a VAX 11/750 and molecular mechanics calculation was done with MM2(87) (Tripos Assoc.Inc. St. Louis) in a 386 personal computer with mathematical co-processor.

see Figs.1 and 2 or in the personal computer using PLOT88 (Plotworks Inc., Ramona).

## 3 The model

Figure 1 shows an schematic diagram of trehalose used in the simulation.

For molecular dynamics simulations united atoms were considered for OH and OH2. Bond length were fixed and the 4C1 ring conformation of each monomer was kept by using improper torsion potential. No torsional potential were used for the atoms involved in the glycosidic linkage nor for the alcohol groups. Force field parameters correspond to the used by Brady [4] for glucose and atom charges were reduced 1/10 from the data provided by him. This reduction introduces an 'effective' dielectric constant of the environment of 100, and is necessary since the original charges were used with explicit water molecules in the system. United atoms bear the net charge of all its components. Only one molecule was simulated in an infinite box at constant temperature.

For the mass weighted molecular dynamics the atoms masses and temperature were scaled ( $m_i = \omega m_i$ ,  $T' = \omega T$ ). Bond angle potential constants were also increased.

The molecular mechanics calculation were done using the force field provided by the MM2(87) and explicit hydrogens. It is worth to note that the glycosidic linkage angles here are affected by a torsion potential. Charges are the same as in MD.

## 4 Results and Discussion

Figure 2a) shows the trajectory of dihedral angles  $\Phi$  (C2a-C1a-O6-C1b) and  $\Psi$  (C2b-C1b-O6-C1a) for a molecular dynamics run of 100 ps after equilibration. Only a limited number of points are taken for the plot. Averaging over 100 ps we have  $\Phi = 224.9$  (RMS= 14.8) and  $\Psi = 224.7$  (RMS=15.8).

During the 100 ps only one conformation is accessed (besides the obvious fluctuations). This may be due to the true existence of only one probable conformation or the low transition probability. Recently Mso *et al* [2] [3] have introduced a mass-weighted molecular dynamics method for the

Figure 3:

rotations become larger and, therefore, the probability of crossing energy barriers increase. As a result, for a given simulation time the available conformations are more easily accessed. An increases in the force constant of angle and bond potentials is necessary.

We have performed MWMD for the same model of trehalose fixing the scale parameter  $\omega = 10$  and the bond angle potential constant equals to 4000.0 kcal/mol/rad<sup>2</sup>. Bond length were, as in MD, kept fixed using the SAHKE procedures.

Figure 2b shows the  $\phi$  and  $\psi$  trajectories during 100 ps for the MWMD simulation. Even for this case both angles fluctuates around a single value, which means that only one predominant conformation is accessed. The sample frequency for plotting produces a partial filtering of fast movements showing clearly that the low frequency fluctuation for both angles are out of phase. This effect seems to appear also observed for the regular MD, although it is not easily observed in fig. 2a).

A total number of 144 conformation were considered for minimizing the energy with MM2. The pair of angles  $\phi$ ,  $\psi$  were fixed and then search for minimum energy adjusting the rest of the geometry. This procedure is part of the options of MM2 program. A 3D plot of the results is shown in figure 3.

The global minimum corresponds to  $\phi = 200.4$  and  $\psi = 198.2$  with  $E = 21.57$  Kcal/mol. Figure 4 shows the contour plot of the same data in which a number of angle trajectories of MD conformations are superimposed.

The agreement between MD and MM good, in spite of the different force fields. It is important to noted that the discrepancy may be due to the fact that the torsion potentials of MM2 have a minimum at  $180^\circ$  while for MD the torsion potentials become only form atom-atom interaction. In the case MM2 the existence of a relative deep well in the torsion potentials may force the equilibrium to lower values. This bias in the results is the reason for which we claim against the use of torsional potentials in performing conformational analysis [5],[6], [1]. Another source of discrepancy may be the rigidity of the monomers in the MD simulation. Having the units in one rigid conformation does not decreases the computer time per time step, however we adopt this approach in order to restrict the conformation analysis to the movement of glycosidic linkage.

The computer time for 100 ps MD simulation is of the order of 300 minutes and 540 for MWMD in a 386 machine with mathematical co-processor 323 minutes. A benchmark for these machines gives about six time faster processing in the 386 compared with the VAX/750, i.e. the complete map will takes about 2000 minutes in the VAX.

## 5 Conclusions

Either molecular dynamics and molecular mechanics seems to provide the same results of the most probable conformation of trehalose. This conformation is not critical dependent on the force field, as has been reported earlier [7]. Molecular dynamics have the obvious advantage of giving detailed information on the flexibility of the molecule and, comparing the computer time of one and another method, seems to be the better option. It has been shown that conformation of polyalcohols is strongly dependent on the nature of solvent explicit included in the simulation [6]. This situation should be tested for oligo and polysaccharides and is being done for trehalose in our laboratory.

## 6 Acknowledgements

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### Figure captions

Fig. 1. Scheme of trehalose. Hydrogen atoms are omitted.

Fig. 2. Trajectories of  $\Phi$  and  $\Psi$  during 100 ps simulation for: a) Molecular Dynamics (MD); b) Mass weighted molecular dynamics (MWMD).

Fig 3. Three dimensional plot of the energy surface for trehalose in function of the two characteristics dihedral.

Fig. 4. Contour plot of the energy surface obtained from MM2 and part of dihedral trajectories obtained by MD. The cross indicates the global minimum obtained by MM2, energies in Kcal/mol.

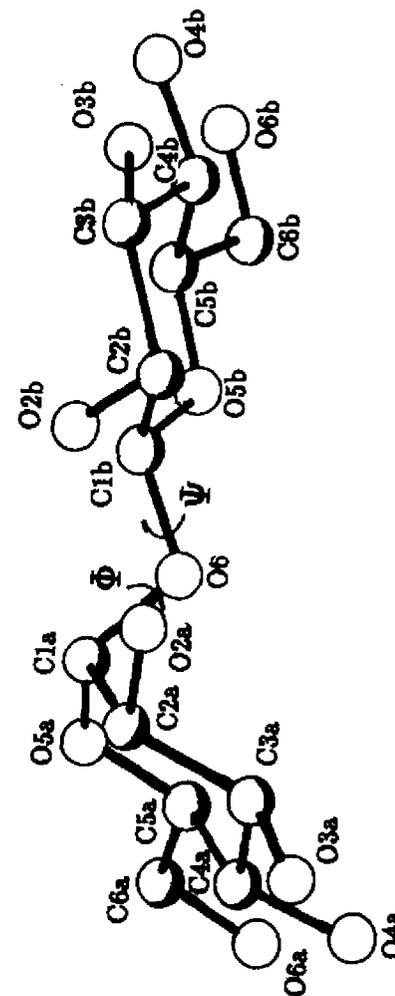


Fig. 1

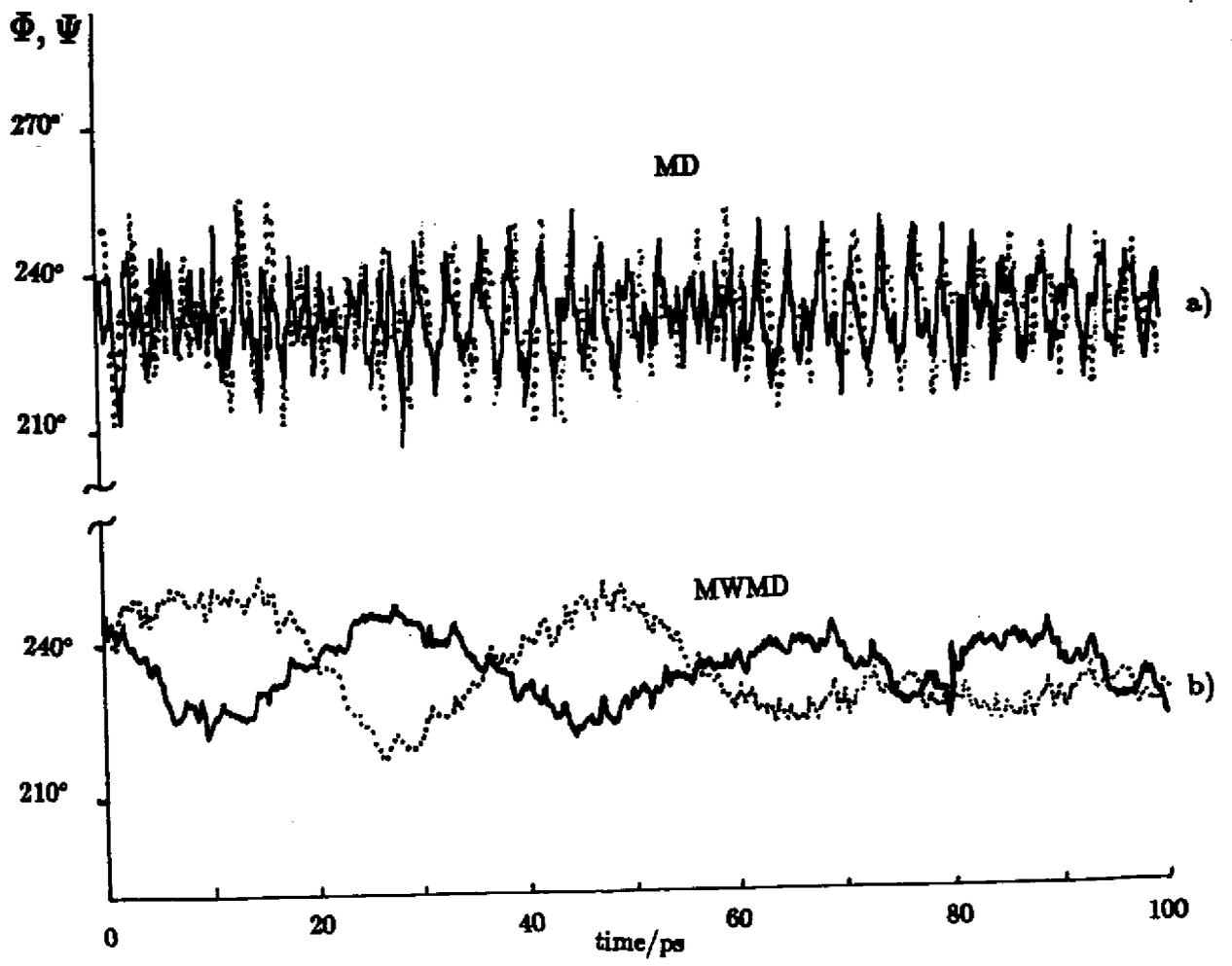


Fig. 2

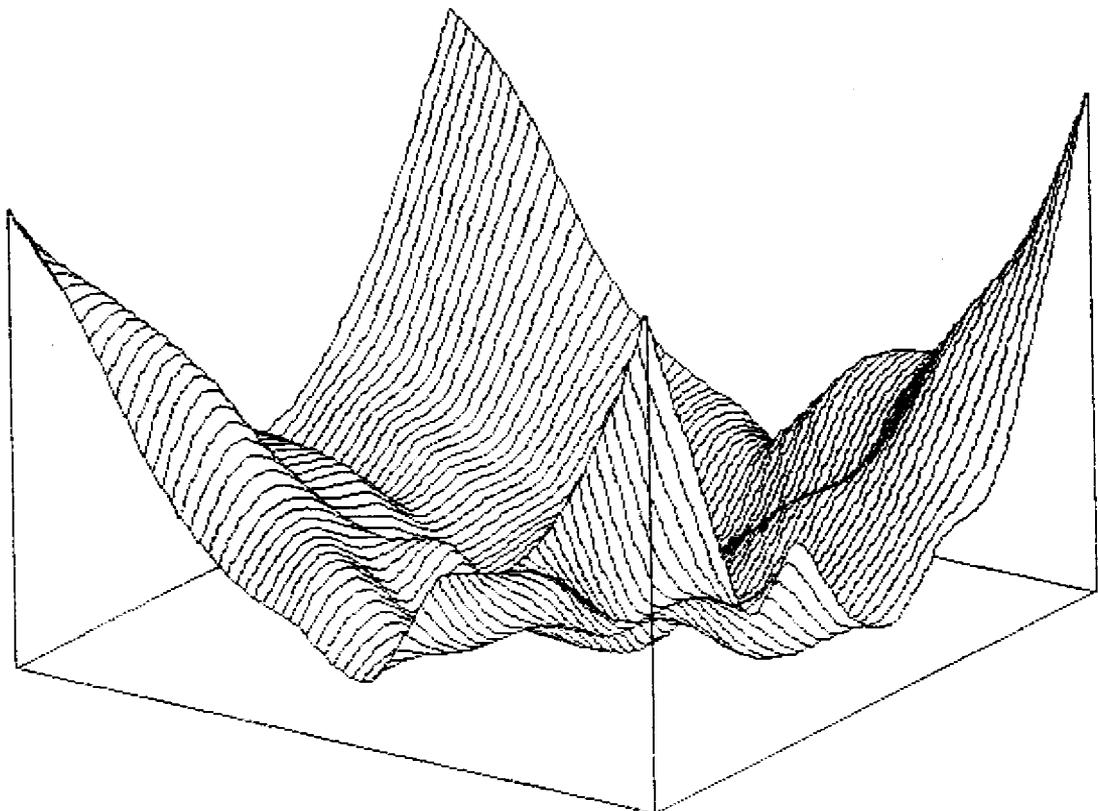


Fig. 3

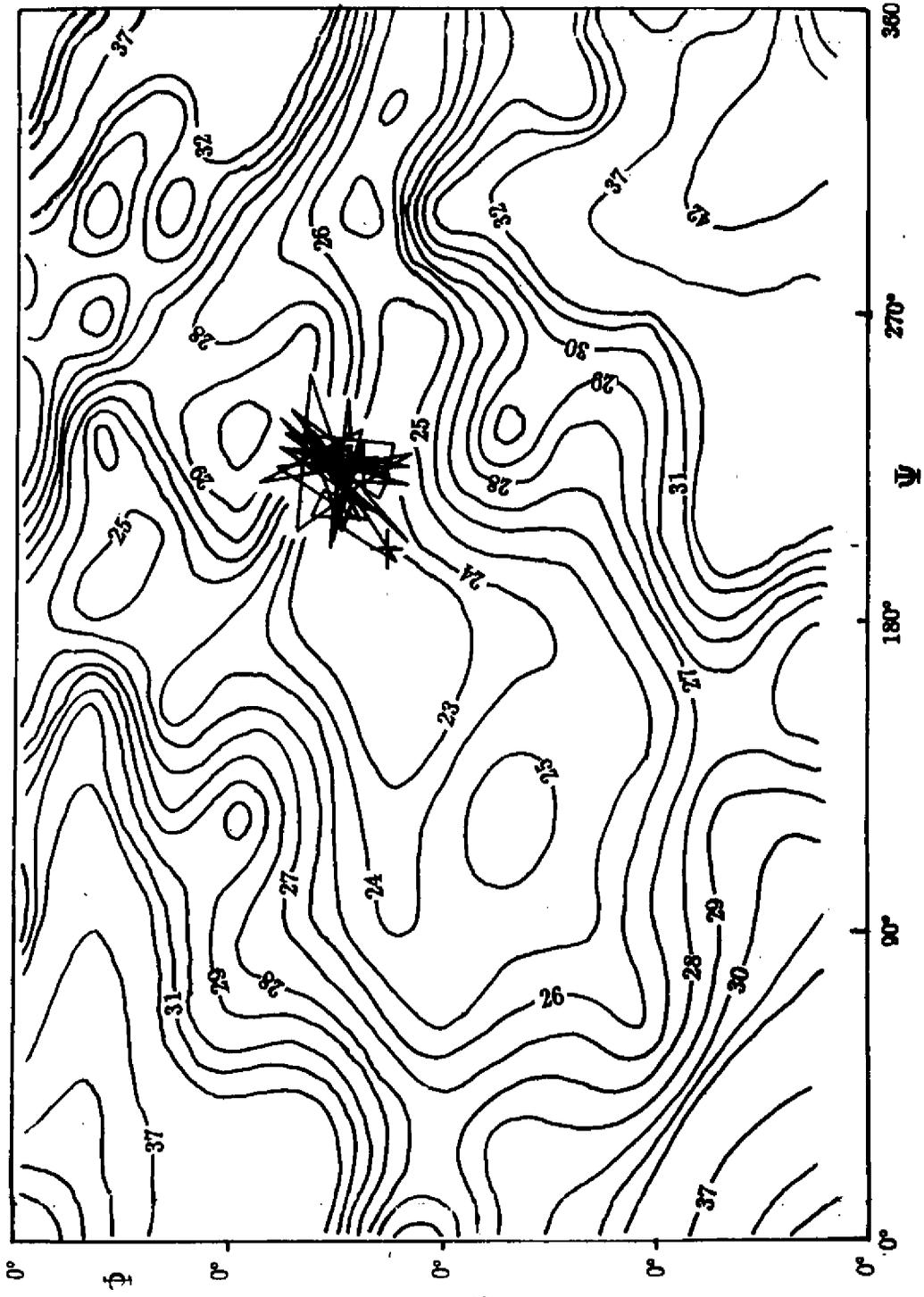


Fig. 4