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Energy Minimization and Conformation Analysis of Molecules using Steepest Descent Method

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Abstract: Function optimization is a calculation that pervades much of numerical analysis. In the context of macromolecules, the function to be optimized (minimized) is an energy. The goal of energy minimization is simply to find the local energy minimum. The energy at this local minimum may be much higher than the energy of the global minimum. Physically, energy minimization corresponds to an instantaneous freezing of the system; a static structure in which no atom feels a net force corresponds to a temperature of 0 K. The potential energy calculated by summing the energies of various interactions is a numerical value for a single conformation. Energy minimization is usually performed by gradient optimization: Here we using steepest descent method: atoms are moved so as to reduce the net forces on them. The minimized structure has small forces on each atom and therefore serves as an excellent starting point for molecular dynamics simulations.

Keywords: Steepest descent, energy minimization, conformation, Molecules,

INTRODUCTION:

About Steepest descent method:

Rather than requiring the calculation of numerous second derivatives, the steepest descent method relies on an approximation. In this method, the second derivative is assumed to be a constant. Therefore, the equation to update the geometry becomes

$$x_{new} = x_{old} - \gamma E'(x_{old}),$$

where γ is a constant. In this method, the gradients at each point still must be calculated, but by not requiring second derivatives to be calculated, the method is much faster per step than the Newton-Raphson method. However, because of the approximation, it is not as efficient and so more steps are generally required to find the minimum.

The method is named Steepest Descent because the direction in which the geometry is first minimized is opposite to the direction in which the gradient is largest (i.e., steepest) at the initial point. Once a minimum in the first direction is reached, a second minimization is carried out starting from that point and moving in the steepest remaining direction. This process continues until a minimum has been reached in all directions to within a sufficient tolerance.

Chemical structures of current oral pharmacological therapies used to treat type 2 diabetes.

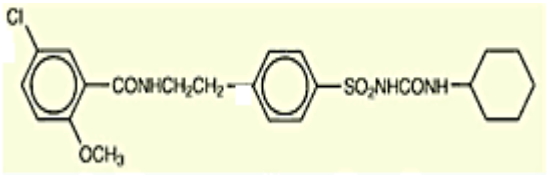

Fig. 1 Glyburide: Number of rotatable bonds – 10

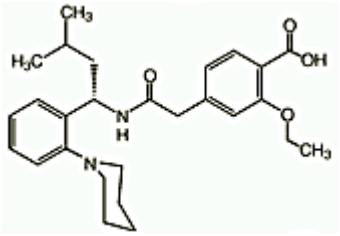

Fig. 2 Repaglinide: Number of rotatable bonds – 8

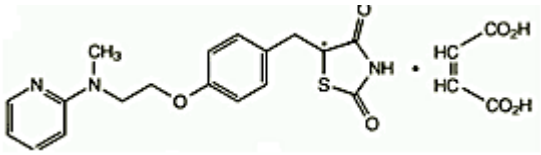

Fig. 3 Rosiglitazone: Number of rotatable bonds -7

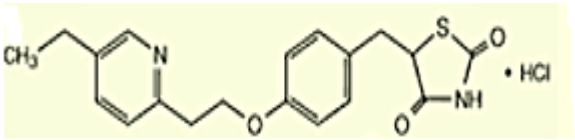

Fig. 4 Pioglitazone: Number of rotatable bonds – 6

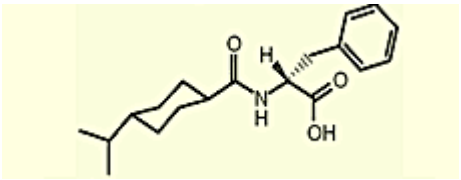

Fig. 5 Nateglinide: Number of rotatable bonds -5

METHODOLOGY:

Around 5 molecules reported as sulfonylureas, meglitinides, metformin, thiazolidinediones, glucosidase inhibitors are considered to study the effect and importance of energy minimization and conformational search analysis using CaChe 6.1.12 software.

In order to perform analysis on a set of molecules described above, rotatable bond counts were made for each molecule. As the energy and conformation of a molecule depends on the number of freely rotatable bonds, the calculation was carried out using CaChe.

Number of freely rotatable bonds are counted using CaChe 'geometry label wizard'. List of type-2 diabetes molecules with rotatable bonds are given as follows. An example of molecule-1 image showing geometry label was given below.

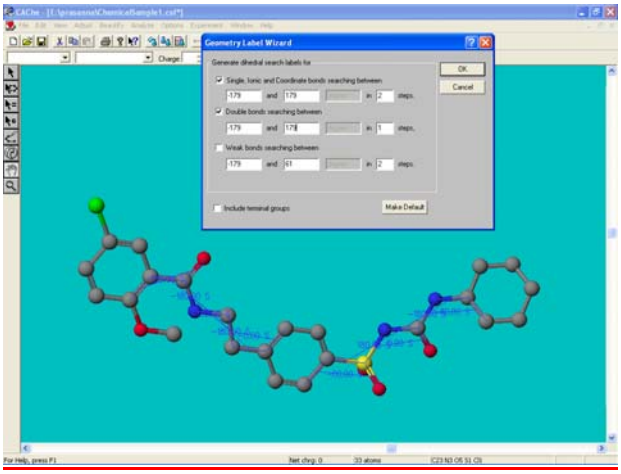

Fig. 6 Image showing geometry label of the molecule

ENERGY MINIMIZATION USING STEEPEST DESCENT METHOD:

Here are some molecular mechanics calculation was carried out for glyburide and repaglinide:

GLYBURIDE

A molecular mechanics calculation was carried out for Chemical sample glyburide steep.csf.

The molecule structure file contains 33 atoms, 35 bonds, and 244 connectors.

MM3 force field

Energy terms for the following interactions are included:

bond stretch
bond angle
dihedral angle
improper torsion
torsion stretch
bend bend
van der Waals
electrostatics
hydrogen bond

Steepest descent search was used to locate the energy minimum.

All atoms are moved at once during minimization.

Van der Waals interactions between atoms separated by greater than 9.00A will be excluded.

Optimization continues until the energy change was less than 0.00100000 kcal/mol,
or until the molecule has been updated 300 times.

The augmented force field is used for the bond stretch, bond angle, dihedral angle and improper torsion interactions.

3 organic ring(s) found in system, 1 ring(s) are found to be aromatic

The energy of the initial structure was 157.3633 kcal/mol.

The energy of the final structure was 29.5239 kcal/mol.

REPAGLINIDE

A molecular mechanics calculation was carried out for Chemical sample repaglinide steep.csf.

The molecule structure file contains 33 atoms, 35 bonds, and 243 connectors.

MM3 force field

Energy terms for the following interactions are included:

bond stretch
bond angle
dihedral angle
improper torsion
torsion stretch
bend bend
van der Waals
electrostatics
hydrogen bond

Steepest descent search was used to locate the energy minimum.

All atoms are moved at once during minimization.

Van der Waals interactions between atoms separated by greater than 9.00A will be excluded.

Optimization continues until the energy change was less than 0.00100000 kcal/mol,
or until the molecule has been updated 300 times.

The augmented force field was used for the bond stretch, bond angle, dihedral angle and improper torsion interactions.

3 organic ring(s) found in system, 1 ring(s) are found to be aromatic

The energy of the initial structure was 75.9242 kcal/mol.

The energy of the final structure was 24.5338 kcal/mol.

NAME OF THE STRUCTURE	Number of Rotatable bonds	STEEPEST DESCENT ALGORITHM ENEGRY (Kcal/mol)	
		BEFORE	AFTER
NATEGLINIDE	5	40.2142	6.6922
PIOGLITAZONE	6	21.1713	3.6017
ROSIGLITAZONE	7	11.0977	6.3203
REPAGLINIDE	8	75.9242	24.5338
GLYBURIDE	10	157.3633	29.5239

Table 1**:** Energy minimization algorithms displaying energy states of five molecules before and after minimization steps using Steepest descent method.

CONFORMATION ANALYSIS FOR PIOGLITAZONE, NATEGLINIDE: PIOGLITAZONE –STEEPEST DESCENT METHOD

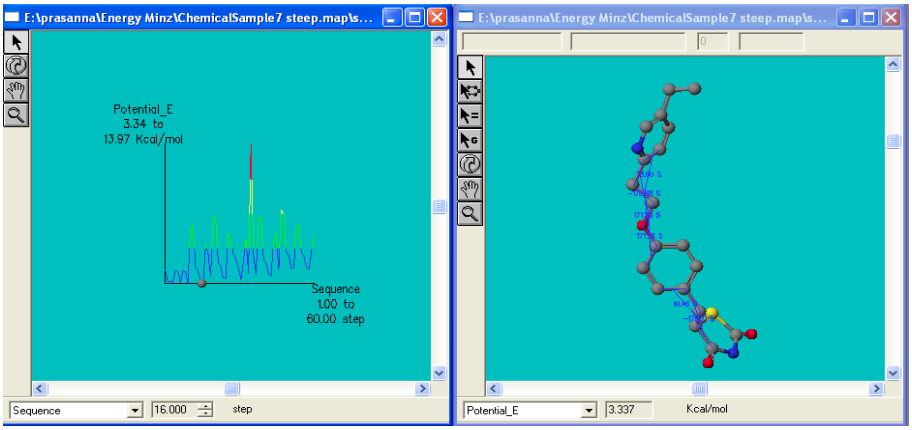

Figure 14: Conformation analysis (potential energy map) of Pioglitazone showing energy minimized structure (local minima).

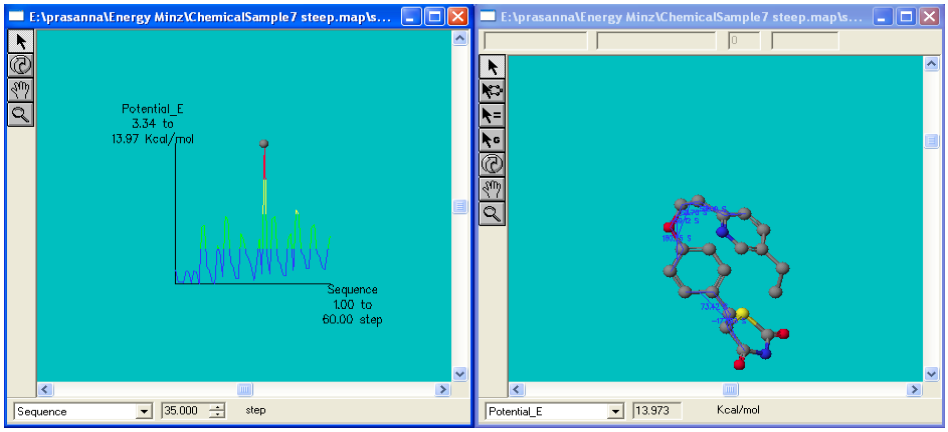

Figure 15: conformation analysis (potential energy map) of Pioglitazone showing energy minimized structure (saddli point).

NATEGLINIDE - STEEPEST DESCENT METHOD

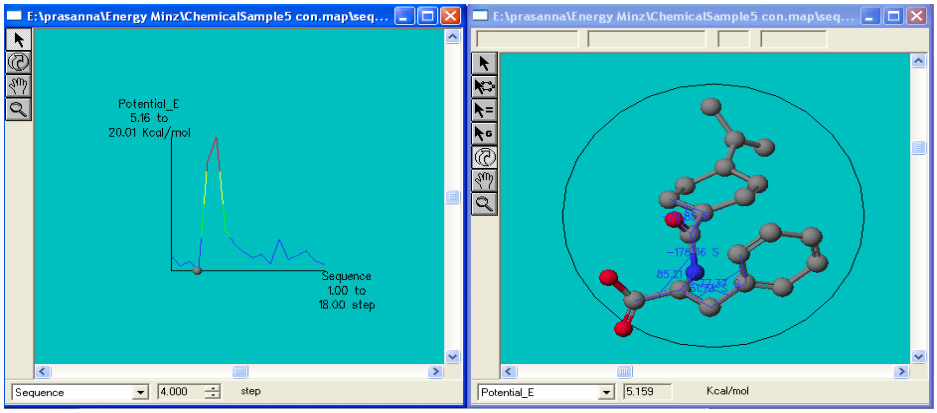

Figure 8: Conformation analysis (potential energy map) of Nateglinide showing energy minimized structure (local minima).

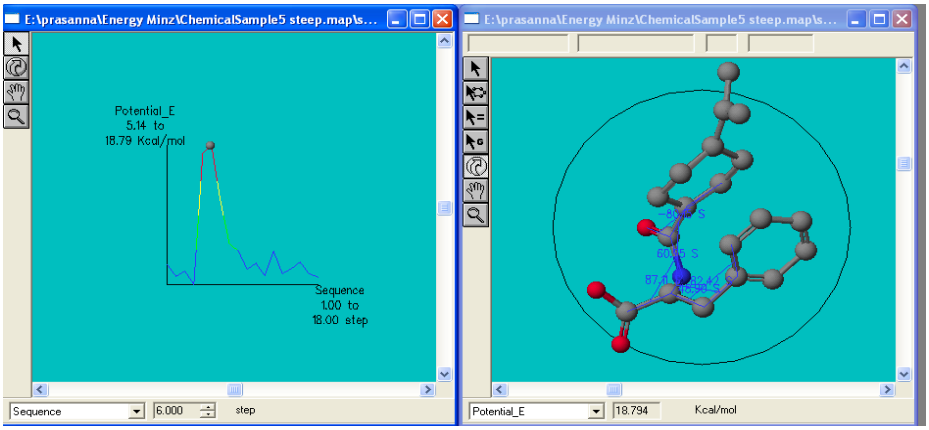

Figure 9: conformation analysis (potential energy map) of Nateglinide showing energy minimized structure(local maxima).

NAME OF THE STRUCTURE	STEEPEST ALGORITHM	
	Energy Minimization	Conformation Analysis
Nateglinide	6.6922	5.159
Pioglitazone	3.6017	3.337
Rosiglitazone	6.3203	5.377
Repaglinide	24.5338	16.839
Glyburide	29.5239	21.876

Table 2: Conformational energy minimized structure data for five molecules using Steepest descent algorithm

CONCLUSION:

From the tables of energy minimization and conformation analysis with varied algorithms it has been shown that the molecules energy lowest when the Steepest descent algorithm was used during energy minimization technique.

REFERENCES:

1. I.A. stepanov, dependence of the energy of molecules on interatomic distance at large distances**,** Computer Modelling and New Technologies, 2006, Vol.10, No.1, 28-30 Transport and Telecommunication Institute, Lomonosov 1, LV-1019, Riga, Latvia
2. http://www.glenbrook.k12.il.us/gbssci/phys/Class/energy/u5l1b.html
3. http://www.ch.embnet.org/MD_tutorial/pages/MD.Part2.html
4. http://cmm.cit.nih.gov/intro_simulation/node22.html
5. http://www.wag.caltech.edu/publications/theses/alan/subsection1_4_0_2_2.html
6. http://www.diabetes.org/type-2-diabetes/oral-medications.jsp
7. http://www.mayoclinic.com/health/diabetes-treatment/DA00089
8. http://diabetes.about.com/
9. Chapter 14 - Joseph L. Evans, Ph.D. and Robert J. Rushakoff, M.D**.** August 26, 2002, oral pharmacological agents for type 2 diabetes: sulfonylureas, meglitinides, metformin, thiazolidinediones, a-glucosidase inhibitors, and emerging approaches
10. http://www.ccdc.cam.ac.uk/support/documentation/silver/1_0/doc/silver_portable-1-071.htmlhttp://bioserv.rpbs.jussieu.fr/Help/FAFDrugs.html]
11. http://cnx.org/content/m11624/latest/]
12. http://www.csb.yale.edu/userguides/datamanip/dock/DOCK_4.0.1/html/Manual.f.html