

This article was downloaded by:

On: 14 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Molecular Simulation

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713644482>

Triglyceride reference database: large scale storage of 3D triglyceride conformers and web-based analysis tools

K. D. Dimakopoulos^a; D. G. Papageorgiou^b; I. N. Demetropoulos^a

^a Department of Chemistry, University of Ioannina, Ioannina, Greece ^b Department of Materials Science and Engineering, University of Ioannina, Ioannina, Greece

To cite this Article Dimakopoulos, K. D. , Papageorgiou, D. G. and Demetropoulos, I. N.(2007) 'Triglyceride reference database: large scale storage of 3D triglyceride conformers and web-based analysis tools', *Molecular Simulation*, 33: 13, 1057 – 1059

To link to this Article: DOI: 10.1080/08927020701579337

URL: <http://dx.doi.org/10.1080/08927020701579337>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Triglyceride reference database: large scale storage of 3D triglyceride conformers and web-based analysis tools

K. D. DIMAKOPOULOS[†], D. G. PAPAGEORGIOU[‡] and I. N. DEMETROPOULOS^{†¶*}

[†]Department of Chemistry, University of Ioannina, Ioannina GR 45110, Greece

[‡]Department of Materials Science and Engineering, University of Ioannina, Ioannina GR 45110, Greece

[¶]Section of Applied Informatics, Department of Information and Telecommunications Engineering, University of West Macedonia, Kozani GR 50100, Greece

(Received May 2007; in final form July 2007)

The Triglyceride Reference Database (TRDB) contains conformer libraries of two triglycerides (tributyrin and triacetin) optimized at various levels of theory. The purpose of the TRDB project and its accompanying interface is to generate, store, process and retrieve triglyceride conformers; hence, it addresses problems and questions concerning geometrical properties, or relative conformer energies, that are of importance (among other uses) to force field evaluations.

Keywords: Tributyrin; Triacetin; Conformer libraries; Database;

1. Introduction

Lipids have a variety of biological functions: they serve as fuel molecules, signal molecules and components of membranes. Triglycerides play a major role in the production of renewable fuels [1] while current medical research focuses on tributyrin as an inhibitor of cancer cell growth [2].

The purpose of the Triglyceride Reference Database (TRDB) project is to generate, store, process and retrieve triglyceride conformers by means of an on-line interactive mechanism, utilizing open source tools.

Literature on systematical storage of rotamer information began as early as 1970 and continues at an accelerated pace. This approach has an advantage over traditional methods in that it uses a database framework that is relational while storage is distributed. These features prove to be of importance as the number of molecular entities increases, and the queries become more complex.

Potential uses of the TRDB include: (a) force field evaluation for triglycerides; (b) effects within homologous series, such as structural patterns that persist or vanish; (c) the performance of detailed studies of the procedures and methods of lipid hydrolysis.

At present the TRDB contains conformer libraries of two triglycerides, namely tributyrin and triacetin, optimized at various levels of theory.

2. Application overview

In order to populate TRDB with the triacetin library we resorted to a grid search procedure in internal coordinate space. For each torsion angle we chose a small set of starting values using previous results on triglycerides. By systematically taking all possible combinations of the starting values for all torsion angles, we created an initial set of structures. Subsequently, every structure was optimized using the Tinker [5] set of tools and MM2 (91) force field, to an RMS gradient of 10^{-6} . The tributyrin library was built by a similar grid search procedure. Previous results [4] using random search methods, as well as MP2 calculations on the triacetin molecule, are also included in the TRDB. At present approximately 1,000,000 triglyceride conformers are stored in the TRDB.

A thorough description of the methods used, although important, is omitted at this stage as we focus on the interface provided.

*Corresponding author. Email: idimitr@cc.uoi.gr; dpapageo@cc.uoi.gr

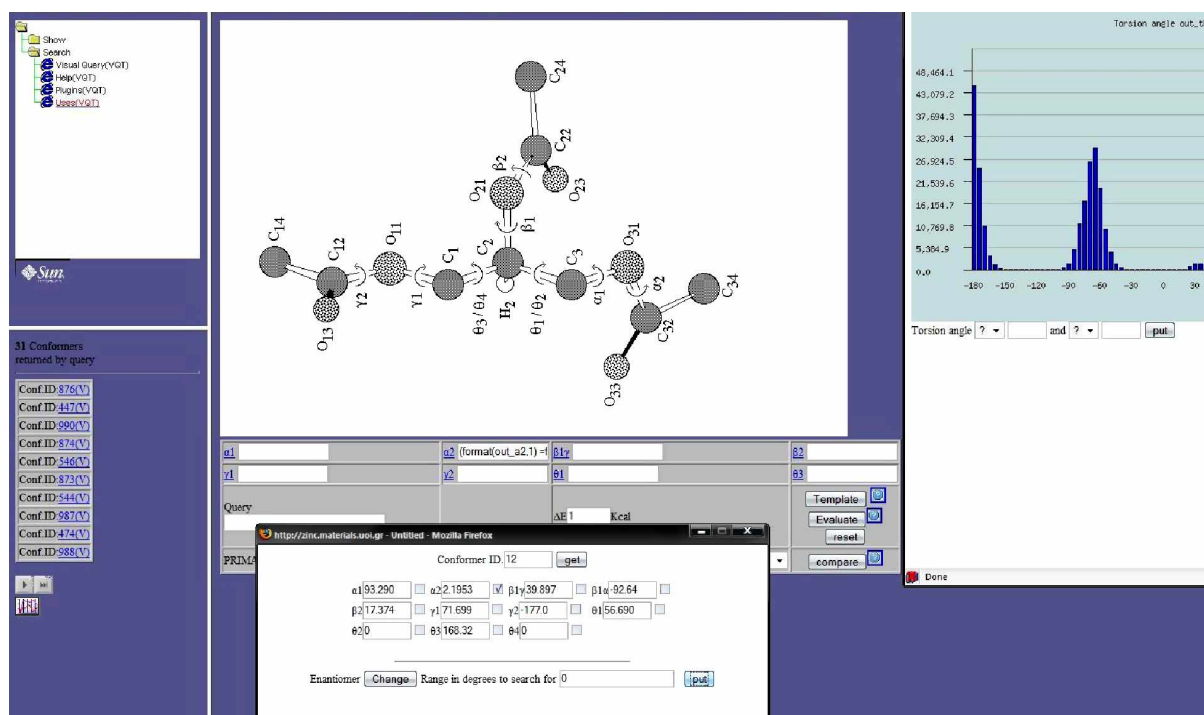


Figure 1. The VQT interface.

Access to the TRDB is facilitated by means of a Visual Query Tool (VQT) as shown in figure 1. A user can make simple or complex queries by visually selecting torsion angles and restricting their respective ranges, utilizing a “torsion angle distribution graph”. The relative strain energy, along with the torsion angles of a particular conformer is provided to assist in making more flexible queries.

The query results are presented in a separate form of the main browser window grouped and arranged by their respective strain energy. The user can visually inspect the results of the query, as well as compare results across libraries. Selected structures can be exported in the form of a PDB file.

All triglyceride conformers are stored and managed by the MySQL (Mysql relational Database, <http://www.mysql.com/>) open source Relational DataBase Management System (RDBMS).

Yearly updates to the current implementation will include the addition of other triglycerides' libraries (such as glycerol triformate, tripropionin, and trivalerin) utilizing molecular mechanics, *ab initio* methods, and the addition of query tools.

The application is available at <http://zinc.materials.uoi.gr/chemtz/>, and is accessible by a Java enabled web browser (Mozilla or Internet Explorer). It includes a short manual, and is free for academic use.

3. Examples

Using VQT we can search for tributyrin conformers abiding to certain similarity criteria with respect to a molecular

template. As an example we examine the lipolytic enzyme cutinase [3] (1OXM), which has a lipid analogue (TC4) embedded in the active site crevice. We use the backbone torsion angles of the lipid analogue part of TC4 to acquire similar tributyrin conformers from the TRDB. Two structures are considered similar when the difference in their respective torsion angles is below a certain threshold. A query with a maximum allowed distance of $\pm 21^\circ$ yielded two conformers similar to TC4. Additionally, a third conformer corresponding to the transition state between the other two was located by utilizing the Tinker set of tools.

These three conformers were carefully positioned inside the protein pocket one at a time, in place of the lipid analogue TC4. A geometrical optimization followed, while the rest of the protein was kept fixed. The protein environment acted as a force field altering simultaneously a number of torsion angles, leading to what appeared to be a “barrier-less” transformation of the triglyceride. All three conformers appear to develop a hydrogen bond network with the catalytic triad.

Another study across the libraries of triacetin and tributyrin, using the tools provided, reveals that the maximum rms distance of all triacetin's skeleton's torsion angles is 4.4° (triacetin MM2(91) versus triacetin MP2/6-31G*), while the maximum difference of any torsion of the same rotamer in the two libraries is found to be 10° . Similarly, the global minimum of triacetin's conformers matches with 4 tributyrin's conformers (triacetin MM2(91), tributyrin MM2(91)), having almost identical skeleton (within 1°); another 316 conformers deviate 10° . This appears to provide useful feedback on how to improve force field parameters.

All these examples are discussed in more detail in the VQT on-line help.

Acknowledgements

This work is supported by the “Academic Equipment Grant program” award No EDUD-7832-010325-GR from “Sun Microsystems”. One of the authors (IND) would like to acknowledge the support of the European Commission through TMR grant number ERB FMGE CT950051.

References

- [1] K.D. Maher, D.C. Bressler. Pyrolysis of triglyceride materials for the production of renewable fuels and chemicals. *Bioresour. Technol.*, **98**, 2351 (2007).
- [2] J. Yan, Y.-H. Xu. Tributyrin inhibits human gastric cancer SGC-7901 cell growth by inducing apoptosis and DNA synthesis arrest. *World J. Gastroenterol.*, **9**(4), 660 (2003).
- [3] S. Longhi, M. Manesse, *et al.* Crystal structure of cutinase covalently inhibited by a triglyceride analogue. *Protein Sci.*, **6**, 275 (1997).
- [4] D.G. Papageorgiou, I.N. Demetropoulos, *et al.* How many conformers of 1,2,3-propanetriol triacetate are present in gas phase and in aqueous solution? *Tetrahedron*, **52**, 677 (1996).
- [5] J.W. Ponder, F.M. Richards. Tinker package. *J. Comput. Chem.*, **8**, 1016 (1987).