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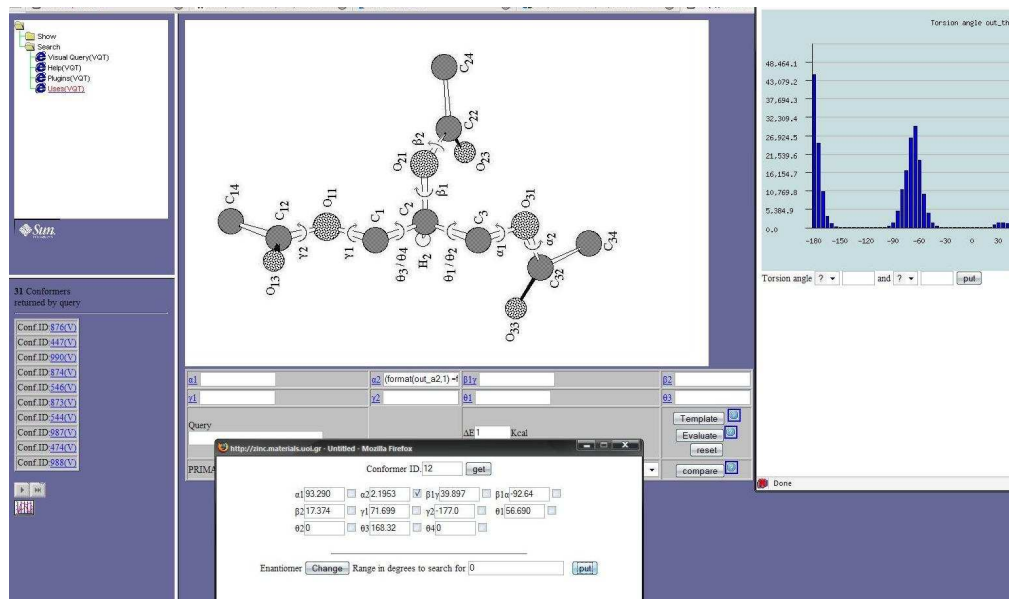


Figure 1. The VQT Interface  
405x241mm (96 x 96 DPI)

# Triglyceride Reference Database: Large scale storage of 3D triglyceride conformers and web-based analysis tools.

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## 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) 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.

[Insert Figure 1 about here]

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 [6] 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.

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2  
3 These three conformers were carefully positioned inside the protein pocket one at a time, in place of  
4 the lipid analogue TC4. A geometrical optimization followed, while the rest of the protein was kept  
5 fixed. The protein environment acted as a force field altering simultaneously a number of torsion  
6 angles, leading to what appeared to be a “barrier-less” transformation of the triglyceride. All three  
7 conformers appear to develop a hydrogen bond network with the catalytic triad.

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

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

### 16 17 **Acknowledgment**

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Figure 1. The VQT Interface

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