JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

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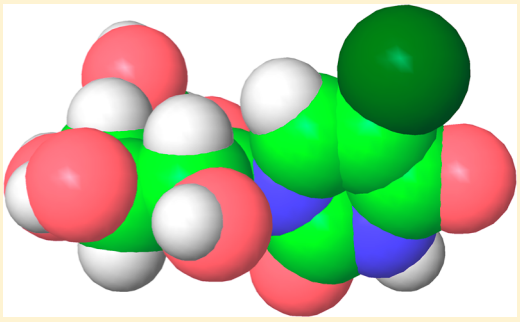
An Integrated Visualization and Basic Molecular Modeling Laboratory for First-Year Undergraduate Medicinal Chemistry

Joseph M. Hayes*

Centre for Materials Science, Division of Chemistry, University of Central Lancashire, Preston PR1 2HE, United Kingdom

Supporting Information

ABSTRACT: A 3D model visualization and basic molecular modeling laboratory suitable for first-year undergraduates studying introductory medicinal chemistry is presented. The 2 h practical is embedded within a series of lectures on drug design, target−drug interactions, enzymes, receptors, nucleic acids, and basic pharmacokinetics. Serving as a teaching aid to the lecture material, 3D models of biological macromolecules exploiting Schrödinger software and the Maestro graphical user interface (GUI) is explored to enhance student learning. A considerably positive response was received from the participants. Background and details of the laboratory are outlined, while the student handout with answers is included as Supporting Information.



KEYWORDS: *First-Year Undergraduate/General, Biochemistry, Laboratory Instruction, Computer-Based Learning, Computational Chemistry, Medicinal Chemistry, Molecular Modeling*

The importance of molecular modeling in the chemistry undergraduate curriculum is increasingly recognized.[1,2] In the pharmaceutical industry, computer-aided molecular design methods are now an integral part of drug discovery projects.[3,4] Incorporation of molecular modeling into the organic,[5−7] inorganic,[8] and physical chemistry[9] curriculums have all been discussed. In medicinal chemistry, too, molecular modeling provides a valuable teaching aid. For example, positive student feedback was received for a laboratory modeling exercise using the HyperChem program incorporated into a third-year undergraduate module in pharmaceutical science.[10] In the exercises, students used computational methods to explore the conformational properties of drug molecules and related them to the pharmacological activity. Peterson and Cox have integrated computational chemistry into a project-orientated biochemistry laboratory that runs over an entire semester.[11] Scientists at Syracuse University developed a course covering the structural and physical properties of biological macromolecules, also employing the HyperChem package.[12] Molecular modeling to study enzyme mutations in the biochemistry laboratory curriculum has been proposed,[13] while Carvalho et al., using Molecular Modeling Pro and Protein Explorer programs, presented a series of exercises related to structure−activity relationships and different disease targets.[14] There are other examples of the benefits of molecular visualization tools to improve the student learning experience.[15−19] However, most of the published exercises are more suitable at the advanced undergraduate level.

Here, a visualization laboratory is presented that integrates basic molecular modeling into a first-year undergraduate medicinal chemistry module. All students are studying toward a chemistry 3-year BSc or 4-year Masters of Chemistry (MChem) degree. The visualization and modeling together with the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) are employed in an active-learning strategy to assist students in the understanding of DNA and enzyme structural features and the molecular basis of target−drug interactions.[20,21] In essence, structures of the macromolecules can be rotated and translated on screen so that their 3D nature can be understood. The student handout is a list of instructions, but also contains numerous questions encouraging critical thinking and analysis, as well as reinforcing concepts from lectures. A select few of the questions are loosely tied to the practical work at hand, but related to lecture material. Although an instructor should have some experience in visualization and manipulation of 3D models to perform this laboratory, only a basic knowledge of molecular modeling is required.

FORMAT OF THE MEDICINAL CHEMISTRY COURSE

The format of the medicinal chemistry module is shown in Table 1. The laboratory is run as a 2-h laboratory (week 7) within a series of 2-h lectures that run over 10 weeks. The class material is mainly based on chapters 1−6 and 10−11 of Patrick's *Introduction to Medicinal Chemistry*, 4th ed.[22]

SOFTWARE EMPLOYED

The software employed is Schrödinger exploiting the Maestro graphical user interface (GUI).[20] Teaching licenses were obtained for the purpose of the laboratory.

Published: April 15, 2014

Table 1. Outline of the Medicinal Chemistry Module Incorporating This Laboratory[a]

Lecture	Topic	Subtopics
1	Overview of Medicinal Chemistry	Drug targets; process of drug design
2	Target–Drug Interactions	Electrostatic and van der Waals interactions; hydrogen bonds; dipole–dipole, ion–dipole, and induced dipole interactions
3	Protein Structure	Amino acids; primary, secondary, tertiary, and quaternary protein structure
4	Enzymes	Active sites; substrate binding; catalytic role and mechanisms; cofactors; regulation of enzymes; allosteric binding sites
5	Receptors	Role of receptors; neurotransmitters and hormones; receptor activation; ion–channel receptors; G-protein coupled receptors; tyrosine kinase-linked receptors; intracellular receptors
6	Nucleic Acids	DNA: primary, secondary, and tertiary structure, replication. RNA and protein synthesis: structure of RNA, transcription, and translation
7	Molecular Modeling	See text
8	Miscellaneous Drug Targets	Transport proteins; lipid carriers; chain terminators; protein–protein interactions; cell membrane lipids; carbohydrates
9	Pharmacokinetics	Absorption, distribution, metabolism, and excretion
10	Revision	

[a]Each class was 2 h. One class per week.

FEATURES OF LABORATORY

PDB Database

The RCSB PDB database, serving as the information portal to solved biological macromolecular structures, is initially introduced to students in Lecture 1.[21,22] In the laboratory, students explore first-hand the database, together with discovering the methods behind biological structure elucidation.

DNA

For the 3D modeling and structural analysis of DNA, the crystal structure (PDB code: 1BNA) of the synthetic B-DNA dodecamer (CpGpCpGpApApTpTpCpGpCpG) is employed.[23] Consisting of just 12 base pairs, on-screen visualization for the beginner is facilitated (Figure 1). The objective is visual interpretation of the structural features of DNA, reemphasizing the corresponding lecture material.

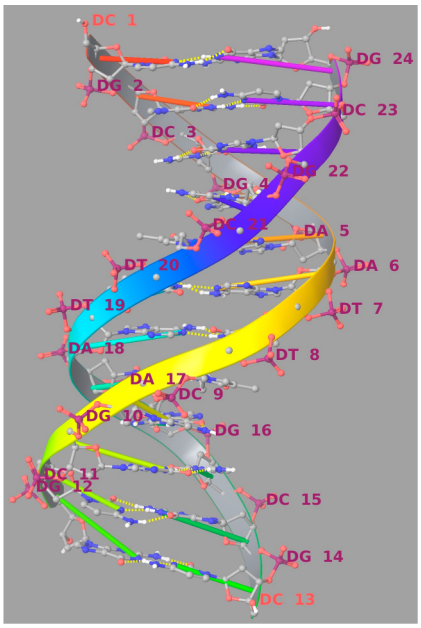


Figure 1. The B-DNA dodecameric structure (PDB code: 1BNA) as viewed by students using Maestro. Labels DA, DT, DG, and DC represent adenine, thymine, guanine, and cytosine nucleic acid bases, respectively.

Glycogen Phosphorylase

The model enzyme is glycogen phosphorylase (GP), see Figure 2. GP is the main regulatory enzyme of the glycogenolysis pathway. Inhibition of hepatic GP is a promising approach to development of new type 2 diabetes treatments.[24,25] GP is an allosteric enzyme and provides a wealth of structural information to be explored that supports Lectures 3 and 4 on protein structure and enzymes, respectively (Table 1).

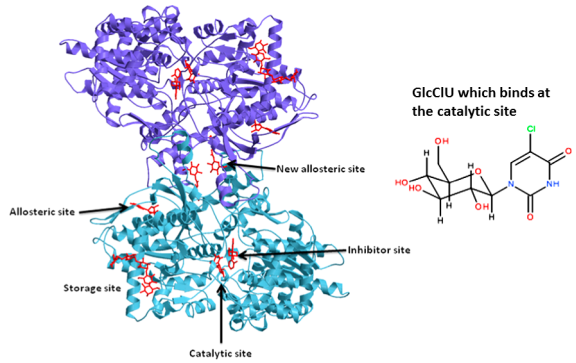


Figure 2. The glycogen phosphorylase dimer highlighting the different binding sites. 1-(β-D-Glucopyranosyl)-5-Cl-uracil (GlcClU) inhibitor, which binds at the catalytic site (PDB code: 3T3E), is also displayed.[26] Image by Demetres D. Leonidas and used with permission.

Structure Based Drug Design (SBDD)

Knowledge of 3D structures of protein–ligand complexes reveals the receptor–ligand interactions critical to ligand recognition and facilitates SBDD. Modeling provides an efficient tool toward exploitation of the known structural data in the design of new inhibitors for experimental evaluation. In the last part of the laboratory, students study binding interactions of 1-(β-D-glucopyranosyl)-5-Cl-uracil (GlcClU) inhibitor bound at the GP catalytic site (Figure 2). This overlaps largely with Lectures 1 and 2 (Table 1).

Pedagogical Goals of Laboratory

The pedagogical goals of the laboratory listed as learning outcomes are shown in Table 2.

dx.doi.org/10.1021/ed400486d | J. Chem. Educ. 2014, 91, 919–923

Table 2. Expected Learning Outcomes of Computational Laboratory

	On successful completion of the laboratory a student will be able to
1	Recognize the methods behind the 3D determination of biomacromolecular structure
2	Identify, define, and describe the key structural features of DNA and enzymes
3	Study and classify target−drug interactions through 3D model visualization
4	Perform basic molecular modeling in terms of "protein preparation" and molecular mechanics minimization
5	Demonstrate a fundamental understanding of the foundations of structure based drug design

EXPERIMENTAL DETAILS

Exploration of the PDB Database

Students become familiar with features of the PDB database such as X-ray crystallography, NMR methods, and electron microscopy as tools for biological macromolecular structure elucidation. Through analysis of statistics, they uncover that X-ray crystallography is by far the most powerful method, and the dramatic rise in the number of solved structures in recent years facilitating SBDD efforts.

DNA Analysis

In the second part, students explore the structural features of DNA. PDB code 1BNA is imported into the Maestro GUI and the structure prepared for visualization and analysis using Schrödinger's "Protein Preparation Wizard".[20] Hydrogens are added to the structure, and bond orders and ionization states are assigned, followed by a constrained minimization of the structure using molecular mechanics (MM) with the OPLS-AA force field. Students explore different atomic representations of the structure, such as "wire" and "ball and stick", as well as the ribbon representation for visualization of secondary structure (Figure 1). Through translation and rotation of the structure on screen, they identify the following (Figure 3):

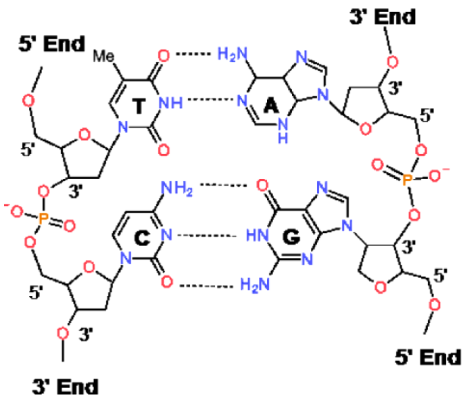


Figure 3. DNA base pairing.

- Components of the DNA backbone
- Base-pairing: A−T (adenine−thymine) and G−C (guanine−cytosine) and the hydrogen bonding involved
- Stacking interactions
- Outward positioning of the ionic phosphate groups so as to interact with water
- DNA major and minor grooves
- 3′ and 5′ ends of the DNA

Glycogen Phosphorylase Analysis

In the next part, students perform structural investigation of the GP:GlcClU complex (PDB code 3T3E; Figure 2). Prior to structural analysis, "Protein Preparation Wizard" is again employed. Analysis of the GP−inhibitor complex is in terms of

- Identification of the different levels of protein structure: primary, secondary, tertiary, and quaternary structure. Through visualization of the structure using ribbons, secondary structure identification is facilitated.
- Determination of the structural components of the GlcClU ligand (sugar linked to a uracil nucleic acid base derivative).
- Isolation of the PLP cofactor location and its classification as a prosthetic group (Figure 4).

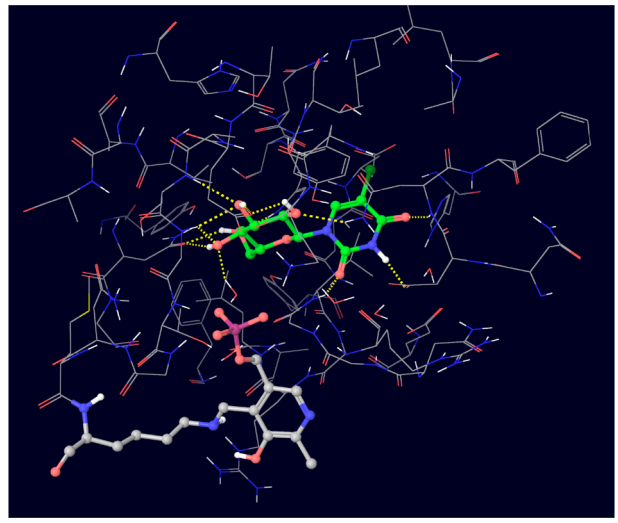


Figure 4. 1-(β-D-Glucopyranosyl)-5-Cl-uracil (GlcClU) ligand bound at the GP catalytic site and its position in relation to the pyridoxal phosphate (PLP) cofactor (displayed in "ball and stick").

- Analysis of enzyme−ligand interactions: identification of residues and their backbone and side-chain atoms involved in hydrogen bond interactions with GlcClU. Students list the residues and atoms (e.g., Ser674 backbone NH). To simplify visualization, only the ligand and residues within 6.5 Å of the ligand are displayed. An idea in future runs of this laboratory is that students also identify and list other types of interactions present, such as van der Waals.
- Proposal of GlcClU structural modifications to improve inhibitor activity and its pharmacokinetic profile in terms of permeability. Examples of other experiments addressing such issues at a more advanced level are available.[14,27]

RESULTS

Logistics

Thirty-one students completed the laboratory. Students worked individually, each with a Hewlett-Packard 2.8 GHz PC running Schrödinger under Windows. The majority of the students needed close to 2 h to complete the experiment. A few students found navigation of the Maestro GUI demanding, given the many different functionalities it supports. Students did have two previous modeling laboratories on a different module, where they were introduced to the building and visualization of 3D

dx.doi.org/10.1021/ed400486d | J. Chem. Educ. 2014, 91, 919−923

models of small organic molecules, and energy minimizations using MM.

Student Feedback

Feedback was considerably positive (Table 3). This was particularly evident under the category of "New Knowledge and Skills" (90.3% positive). Some comments in terms of the latter were "helped greatly in understanding the software and protein structure" and "beneficial, very positive".

Table 3. Student Feedback Responses on the Laboratory[a]

Category	Number of Responses (%)[a]		
	Positive	Neutral	Negative
New Knowledge and Skills	28 (90.3)	3 (9.7)	0 (0.0)
Molecular modeling reinforcing concepts from lectures	22 (71.0)	7 (22.5)	2 (6.5)

[a]31 student respondents.

In terms of modeling serving as an aid to the understanding of key concepts covered in the lectures, 71% were positive. Positive comments included "linked the two very well" and "reinforces all the information from the lectures." The lower positive response was potentially due to some students being somewhat overwhelmed by the number of atoms on view, with one student commenting, "was quite complicated and difficult to understand the molecular shapes." Also, some students had the aforementioned problem with Maestro navigation: "can see the potential, but the program is difficult to navigate."

Student Assessment

There was no formal assessment of student performance in the actual laboratory. Hence, a student-centered approach to learning was applied with participants receiving guidance and prompting throughout. Full answers to the laboratory questions were made available following the practical. The assessment of Lectures 1−10 (including this laboratory) was a written examination with an 87.5% pass rate and an average mark of 62.8% (standard deviation 18.0%). This pass rate and average mark were among the highest (top 2) of the end of module examinations taken by the students in their first year.

CONCLUSION

3D model visualization and basic molecular modeling is presented as a valuable teaching aid in undergraduate introductory medicinal chemistry. A largely positive account of a laboratory incorporated into a first-year module is reported. Although commercial software from Schrödinger with the Maestro GUI was employed, the experimental design was such that most (bio)molecular modeling software could be used. Mainly positive student feedback was received, although a few students were somewhat overwhelmed with the size of the biomacromolecular structures on view, as well as with navigation of the Maestro GUI. With respect to the latter, there is the possibility to use customized, simpler versions of Maestro's menus and toolbars, in particular Maestro Elements that would be more suitable for beginners.[20] In conclusion, through 3D visualization in this laboratory, the majority of students gained a better understanding of structural properties of DNA and enzymes, as well as the general principles that define real life molecular modeling applications, such as in SBDD.

ASSOCIATED CONTENT

Supporting Information

The student handout with answers. This material is available via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jhayes@uclan.ac.uk.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Clauss, A. D.; Nelsen, S. F. Integrating Computational Molecular Modeling into the Undergraduate Organic Chemistry Curriculum. *J. Chem. Educ.* **2009**, *86*, 955−958.
(2) Jones, M. B. Molecular modeling in the undergraduate chemistry curriculum. *J. Chem. Educ.* **2001**, *78*, 867−868.
(3) Yuriev, E.; Ramsland, P. A. Latest developments in molecular docking: 2010−2011 in review. *J. Mol. Recognit.* **2013**, *26*, 215−239.
(4) Prathipati, P.; Dixit, A.; Saxena, A. K. Computer-aided drug design: Integration of structure-based and ligand-based approaches in drug design. *Curr. Comput.-Aided Drug Des.* **2007**, *3*, 133−148.
(5) Lee, M.; Garbiras, B.; Preti, C. An Undergraduate Organic-Synthesis, Spectroscopy, and Molecular Modeling Project - Asymmetric Lewis-Acid Catalyzed Diels-Alder Reaction of Menthyl Acrylate with Cyclopentadiene. *J. Chem. Educ.* **1995**, *72*, 378−380.
(6) Poon, T.; Bodolosky, S. A.; Norris, C. M. An integrated molecular modeling and melting point experiment for the organic chemistry laboratory. *J. Chem. Educ.* **1999**, *76*, 983−985.
(7) Klassen, J. B.; Graham, K. J.; Muldoon, W. P. Molecular modeling as an aid to understanding stereoselectivity. *J. Chem. Educ.* **1999**, *76*, 985−986.
(8) Montgomery, C. D. Integrating molecular modeling into the inorganic chemistry laboratory. *J. Chem. Educ.* **2001**, *78*, 840−844.
(9) Johnson, L. E.; Engel, T. Integrating Computational Chemistry into the Physical Chemistry Curriculum. *J. Chem. Educ.* **2011**, *88*, 569−573.
(10) Yuriev, E.; Chalmers, D.; Capuano, B. Conformational Analysis of Drug Molecules: A Practical Exercise in the Medicinal Chemistry Course. *J. Chem. Educ.* **2009**, *86*, 477−478.
(11) Peterson, R. R.; Cox, J. R. Integrating computational chemistry into a project-oriented biochemistry laboratory experience: A new twist on the lysozyme experiment. *J. Chem. Educ.* **2001**, *78*, 1551−1555.
(12) Dabrowiak, J. C.; Hatala, P. J.; McPike, M. P. A molecular modeling program for teaching structural biochemistry. *J. Chem. Educ.* **2000**, *77*, 397−400.
(13) Wolfson, A. J.; Hall, M. L.; Branham, T. R. An integrated biochemistry laboratory, including molecular modeling. *J. Chem. Educ.* **1996**, *73*, 1026−1029.
(14) Carvalho, I.; Borges, A. D. L.; Bernardes, L. S. C. Medicinal chemistry and molecular modeling: An integration to teach drug structure-activity relationship and the molecular basis of drug action. *J. Chem. Educ.* **2005**, *82*, 588−596.
(15) Bottomley, S.; Chandler, D.; Morgan, E.; Helmerhorst, E. jAMVLE, A New Integrated Molecular Visualization Learning Environment. *Biochem. Mol. Biol. Edu.* **2006**, *34*, 343−349.
(16) Parslow, G. R. Commentary: Molecular visualization tools are good teaching aids when used appropriately. *Biochem. Mol. Biol. Edu.* **2002**, *30*, 128−129.
(17) Weiner, S. W.; Cerpovicz, P. F.; Dixon, D. W.; Harden, D. B.; Hobbs, D. S.; Gosnell, D. L. RasMol and Mage in the undergraduate biochemistry curriculum. *J. Chem. Educ.* **2000**, *77*, 401−406.
(18) Honey, D. W.; Cox, J. R. Lesson plan for protein exploration in a large biochemistry class. *Biochem. Mol. Biol. Edu.* **2003**, *31*, 356−362.

(19) Roy, U.; Luck, L. A. Molecular modeling of estrogen receptor using molecular operating environment. *Biochem. Mol. Biol. Edu.* **2007**, *35*, 238−243.
(20) *Maestro, version 9.3*; Schrödinger, LLC: New York, NY, 2012.
(21) RCSB Protein Data Bank. http://www.rcsb.org/pdb (accessed Mar 2014).
(22) Patrick, G. L. *An Introduction to Medicinal Chemistry*, 4th ed.; Oxford University Press: Oxford, U.K., 2009.
(23) Drew, H. R.; Wing, R. M.; Takano, T.; Broka, C.; Tanaka, S.; Itakura, K.; Dickerson, R. E. Structure of a B-DNA Dodecamer - Conformation and Dynamics 0.1. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 2179−2183.
(24) Hayes, J. M.; Leonidas, D. D. Computation as a Tool for Glycogen Phosphorylase Inhibitor Design. *Mini-Rev. Med. Chem.* **2010**, *10*, 1156−1174.
(25) Somsak, L.; Czifrak, K.; Toth, M.; Bokor, E.; Chrysina, E. D.; Alexacou, K. M.; Hayes, J. M.; Tiraidis, C.; Lazoura, E.; Leonidas, D. D.; Zographos, S. E.; Oikonomakos, N. G. New Inhibitors of Glycogen Phosphorylase as Potential Antidiabetic Agents. *Curr. Med. Chem.* **2008**, *15*, 2933−2983.
(26) Kantsadi, A. L.; Hayes, J. M.; Manta, S.; Skamnaki, V. T.; Kiritsis, C.; Psarra, A. M.; Koutsogiannis, Z.; Dimopoulou, A.; Theofanous, S.; Nikoleousakos, N.; Zoumpoulakis, P.; Kontou, M.; Papadopoulos, G.; Zographos, S. E.; Komiotis, D.; Leonidas, D. D. The sigma-hole phenomenon of halogen atoms forms the structural basis of the strong inhibitory potency of C5 halogen substituted glucopyranosyl nucleosides towards glycogen phosphorylase b. *ChemMedChem.* **2012**, *7*, 722−732.
(27) Sutch, B. T.; Romero, R. M.; Neamati, N.; Haworth, I. S. Integrated Teaching of Structure-Based Drug Design and Biopharmaceutics: A Computer-Based Approach. *J. Chem. Educ.* **2012**, *89*, 45−51.