PC-based molecular modeling in the classroom: Applications to medicinal chemistry and biochemistry

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Among the most difficult aspects of medicinal chemistry and biochemistry for the student to master are the three-dimensional (3D) nature of drugs and bio-organic substances and the interaction of these substances with 3D targets. Compounding this problem is the fact that such relationships are very difficult to illustrate in a lecture or discussion format. While skeletal molecular models serve a useful role in the learning process, the techniques of PC-based desktop molecular visualization provide a more powerful and effective alternative to the lecture format. These techniques can be implemented on standard MS-DOS PC hardware using one of the commonly available data projection systems. The approach has found considerable use in several areas, including the generation of computer-based lecture aids, the illustration of the molecular shapes of drugs and biochemical structures, the superposition and comparison of drug substances with common pharmacophores, and the illustration of enzyme–substrate interactions. Another related technique, molecular animation, has proven to be quite successful at illustrating the essentials of enzyme mechanisms in the classroom. The "film clips" resulting from this technique may have use beyond the classroom, and further work in this area is underway.

Keywords: desktop molecular visualization, molecular animation, stereochemistry, enzyme structure and function, bioisosterism

INTRODUCTION

The use of molecular graphics in its many forms has become a common and nearly essential component of the molecular design process, as evidenced by the considerable number of reports in the recent literature on its use.[1] Molecular graphics and modeling has begun to come of age on microprocessor-based computers as well. A number of software packages now exist for both PC-based (MS-DOS) systems[2] and Macintosh-based systems,[3] as well as others. Progress has been substantial since the first commercial microcomputer-based modeling system was published in 1985, when both 8088-based MS-DOS and Apple II/c/e computers were the norm.[4]

Microcomputer-based modeling and graphics systems seem to have found their greatest use in the research environment, where they can offer a cost-effective alternative to the high-end systems, as long as the compounds under study are small (fewer than 100 atoms). In the instructional realm their use appears to have been more limited. In 1984 we began to investigate the use of molecular graphics for the instruction of chemistry and medicinal chemistry at the undergraduate level.[5] The experiences of the past six years have led me to conclude that such use makes a difference in the learning environment. Microcomputer-based molecular graphics and, more recently, microcomputer-based molecular animation provide insight into a number of areas and processes that cannot be provided otherwise in a lecture or discussion setting. This report details some of the author's experiences in this area and outlines ways that these techniques can be applied to instruction.

GRAPHICS APPLICATIONS IN THE CLASSROOM

Among the most difficult aspects of medicinal chemistry for a student to master are the three-dimensional (3D) nature of drug substances and their interactions with 3D biological targets. These skills are based on the more fundamental stereochemical concepts of organic chemistry, which also can be difficult for students to master. For most students, the primary aid to learning stereochemistry is a set of skeletal molecular models. This is true for both the introductory principles learned in organic chemistry and the more specialized drug superimposability concepts found in medicinal chemistry. Using sets of these physical models, whether simple colored tubes or balls and sticks, students of organic chemistry may gain knowledge of the true spatial shapes of molecules. Students in medicinal chemistry and biochemistry may compare two or more models of drugs or bioorganic molecules and develop considerable insight regarding both the compounds' structural basis of action and their demonstrated side effects.

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The students' difficulty with the concept of 3D structure is exacerbated by the lecture and discussion format used by most schools. Structures drawn on paper or projected on a screen lack the information conveyed in skeletal models, yet it is not realistic to use physical models in a large class and to expect students to grasp the relevant concepts being illustrated. Skeletal models are most useful for either an individual or a very small group, and are least useful in large lecture rooms. When confronted with the need to illustrate the stereochemical aspects of a drug's action or a biochemical entity, an instructor usually produces a visual representation of the structure(s), either on a chalkboard or, more recently, on a slide or overhead transparency. Unfortunately these media are static and, as such, the images they contain cannot reinforce the 3D dynamic character of the molecules under consideration.

One solution to this problem is the use of a computer to represent the structures. Large, sophisticated computer systems are routinely used in the pharmaceutical and other industries, as well as in academic research. While these systems are very impressive and would easily be able to illustrate the relatively simple points of any classroom discussion, they are not particularly well suited for classroom use for a number of reasons. These include their considerable expense, their lack of portability, and the inability to project their screen images to a large classroom audience.

CHARACTERISTICS OF CLASSROOM GRAPHICS SYSTEMS

From a teaching perspective, many of the requirements for a computer-based modeling system for lecture or classroom use are considerably different from those of a system used primarily for research. On the hardware side, the highest central processor speed is always desirable, but this aspect is probably less important in the classroom than it is in research, because structural optimization by computational techniques is not a necessary part of classroom molecular graphics. Also, while the highest resolution graphics display is desirable for research, the commonly accessible EGA or VGA levels of resolution (640 × 350 or 640 × 480 pixels, respectively) is adequate for classroom use. This is fortunate, because the higher resolution displays used by high-end systems are not generally projectable to large groups using readily available projection technology. In my experience, PC-based molecular visualization in the classroom requires the minimum configuration of a 10-MHz 80286-based machine equipped with a hard disk, 512K of memory and EGA-level graphics. A math coprocessor is useful, and a mouse or equivalent device is almost essential, both for structure manipulation and as a pointer for navigating among the molecular images on the screen.

There are several other hardware and software characteristics that are important for use of molecular visualization in the classroom. These include:

(1) Ease of use. The hardware must be easily connectable to standard TV monitors or projection TV systems. The software should be based on contemporary user interface design principles and should be clearly understandable with minimal practice; i.e., it should have a shallow learning curve.

(2) Portability. The hardware must be easily movable into and out of the teaching site. Typically, the instructor has ten minutes before class to set up the computer and ten minutes after class to remove it. The emergence of some of the newer laptop computers has made this task much easier. It is still rare to have a classroom permanently equipped with a microcomputer solely for instructional use.

(3) File management. The software must be able to maintain a series of structural data files, accessing and displaying them on demand. Virtually all currently available software systems have this feature.

(4) Flexible movement of structures. The software must be able to translate a structure in any direction (or at least along any axis), rotate it about any axis or bond, and scale it to fill a display screen. It should do this with a mouse or other device, in an interactive manner, so the instructor does not spend time typing commands instead of interacting with the students.

(5) Discrimination function. The software must be able to handle at least two structures independently, allowing them to be manipulated independently (the "docking" function) or together.

(6) Low cost. The software used in class should be low enough in cost to allow placement of multiple copies in school computer learning laboratories, as well as purchase by individual students, should they desire to do so. In today's market, this means that the software should cost less than $50 per copy after educational discounts.

All of these software characteristics, except perhaps the last, can be met by any one of the several microcomputer-based molecular graphics programs currently on the market, and the choice of one over the other can be based on personal preference and suitability to the individual situation. When we began to investigate this issue in 1984, there was no software of this type on the market, so we developed a package for teaching and research purposes. The software was subsequently marketed by Academic Press for the MS-DOS and Apple II series.[4] The MS-DOS version of the program has evolved into PCMODEL: Molecular Graphics for the PC, which is available as shareware, thus meeting the last of the requirements listed above.

Classroom projection devices

One of the most crucial issues of classroom molecular visualization is the projection of screen images generated by the software, and this issue deserves additional comment. There are a limited number of ways that screen images can be displayed in the classroom, and each approach has both advantages and disadvantages. Probably the most effective display device is a color data projector.[6] These projectors come in both one-lens and three-lens configurations, although the higher end devices are all of the three-lens type. Their advantage is that the entire class can view the computer screen projected in full color, much like the image resulting from a slide projector, only not as bright. The disadvantages of these devices include their initial expense ($8 000–$15 000+) and the fact that they take time to set up. One cannot set up one of these devices for a single class

session, but if a classroom can be permanently equipped with one, it is by far the most desirable of the options available.

An alternate choice for computer screen display is the LCD projection panel.[7] This device is placed on the light table of a standard overhead projector. The computer image appears in a window of the device, and as the light is projected through the window to the screen, the computer image is projected as well. The advantages of these devices include a more reasonable cost ($1 000–$5 000), as well as easy setup and removal from the room. Current models have both EGA and VGA resolution. The disadvantage of these devices is that most models project in black and white only. While some models represent color in shades of gray, others ignore it altogether. The technology of true full-color LCD projection is just now becoming available, but because it is new, the costs are still high. Fortunately, much of the stereochemical information from molecular graphics can be presented without the use of color, so the black-and-white limitation of the less expensive units is not overly restrictive. Under these conditions, however, the molecular graphics software must be able to turn off, or at least alter, the color information present in the normal monitor signal so that the images are displayed effectively by the LCD panel. The software must also be able to distinguish molecules in a display—through different line patterns, for example.

Finally, a third alternative is the use of monitors placed around the room. This is usually not cost-effective, because the monitors must be large and must have at least EGA-level resolution. Providing full coverage of a lecture room with several of these monitors would likely cost more than a single color projection monitor. For smaller rooms however, this option may be worth considering, although one still has the problem of transporting and setting up a heavy device in a limited time. Standard television monitors can project CGA-level resolution images (320 × 200 in 4 colors or 640 × 200 without color), and if this is all one has available it can be marginally effective. Under these conditions the visualization software must be configurable to project a CGA image. (Not all packages are so configurable.)

APPLICATIONS

Once the classroom is equipped with suitable hardware, it may be used for several different instructional activities. Three with which I have had personal experience include molecular graphics, molecular animation, and use of computer-based visuals and lecture aids. The first two of these topics represent the two major forms of desktop molecular visualization, while the last topic provides some additional capability at little additional cost.

Lecture aids

Several commercial programs exist that can function as an electronic slide or transparency projection system.[8] Using such a program, one can create text screens and graphs in much the same way that one creates hard copy slides and overhead transparencies. Most of these packages can place predefined sequences of images on the screen at the touch of a key or a mouse button, much as one would do with a slide projector. The lead time for preparing these images is often much less than for traditional procedures. Moreover, the costs are lower once the equipment is in place, and changes in the material may be made almost instantly, with no further cost to the user.

Molecular shapes of drugs

From a medicinal chemistry perspective, the area of microcomputer-based molecular graphics offers the greatest potential in the instructional environment. I use it routinely for instruction in three different but related ways. One use is to illustrate molecular shape. Certain drug molecules are uniquely shaped due to one or more molecular characteristics, and often these shapes are responsible for both the chemical and therapeutic properties of the drug. An example is the penicillin series of drugs, in which the β-lactam ring system determines in part the unique profile of the drug substances in this series. Color Plate 1 shows the image of benzyl penicillin (penicillin-G), one of the first generation of penicillins that revolutionized antibacterial therapy. The atoms are both color-coded and labeled according to their atomic identities. When viewed in three dimensions the penicillin ring system is dramatically different than the two-dimensional structure usually written on the printed page. Other examples of characteristic molecular shapes among drug molecules (not shown) include chlorpromazine (a classical neuroleptic drug) and imipramine (a classical tricyclic antidepressant drug). These two drugs look quite similar when compared via their two-dimensional formulas, while in three dimensions it is clear that the ring systems are not as similar as they appear in projection form.

Structural biochemistry applications

Another use for molecular shape illustrations is in the discipline of biochemistry. Students in introductory biochemistry courses are taught that enzymes are proteins and that these proteins are characterized by unique arrangements of amino acid sequences. Moreover, these sequences account for the secondary and tertiary structures of the proteins, which are held together by intramolecular hydrogen bonding forces between amide hydrogens and carbonyl oxygens. The characteristic structural entities within proteins, including α-helices and β-structures, need to be seen to be understood. Mere description of their existence and structure is not enough. Color Plates 2 and 3 show a typical α-helix, taken from the Protein Data Bank structure of Dihydrofolate Reductase (EC 1.5.1.3) complexed with methotrexate.[9] As rotation about the y-axis in real time occurs, the view goes from the lateral view (Color Plate 2) to the longitudinal view (Color Plate 3) and back again. Four of the hydrogen bonds are monitored, with the distances printed on the screen, so students can see the source of the forces stabilizing the helix. In the view along the axis of the helix (Color Plate 3), students can see the hollow core and the spiral nature of the helix. They can also readily see the circle of blue nitrogen atoms with the residual side chains radiating from the helix. Similar approaches exist for illustrating the other protein structural components.

Superposition and comparison of drug molecules

A third major use for microcomputer-based molecular graphics is the superposition of two or more molecules with common structural features. It is in this area that the interactive character of the microcomputer and its software really pays off. One of the principles of medicinal chemistry holds that drugs owe their activities to the existence of unique pharmacophores (stereochemical arrangements of specific functional groups), which interact with specific target macromolecular sites within the organism. It is to be expected, then, that series of drugs with therapeutic effects in common would also have structural features in common. Often these structural commonalities are obvious, but seemingly just as often they are not. The concepts of bioisosterism[10] allow for wide substitution of functional groups without changing the nature of the interaction between the target and the drug.

To illustrate the superposition principle used in the classroom, we can examine a very simple case, a comparison of the neurotransmitter acetylcholine with a toxic natural product, muscarine (Color Plate 4). The comparison begins by examining the two structures independently, rotating them interactively to provide the depth cues necessary to grasp their 3D character. Acetylcholine is a labile, acyclic substance containing a quaternary ammonium group and an acetate ester function separated by an ethylene bridge. It is shown at the left side of Color Plate 4. Muscarine also contains a quaternary ammonium group, but no ester function. Instead, it contains a trisubstituted tetrahydrofuran moiety. Its structure is shown at the right side of Color Plate 4. Most of the hydrogens in both molecules have been masked under software control to reduce the complexity of the images. We then point out that for both substances to be agonists, the common points of the molecule must bind to the common sites at the receptor. The charged nitrogen is an obvious common point. Other common points are less obvious to the student who may be unaccustomed to thinking in three dimensions. To aid in visualizing the relationship between the two molecules, the muscarine molecule is displayed in a highlighting color and its bonds are converted to dotted lines. Under these conditions the images are sufficiently different that they are easily discriminated under all projection conditions, with or without color. One of the molecules is connected to the mouse and moved in real time to superimpose upon the other one. The mouse is then reconnected to the aggregate and rotation is continued to show that they in fact demonstrate a very close fit. The end result of this process appears in Color Plate 5.

A more complex example is shown in Color Plate 6. The well-known analgetic (and abuse) drug, morphine, has been the prototype drug for the design of a number of synthetic analogs, most of which contains a partial structure of the morphine molecule. Meperidine is one such drug. Over the years there has been considerable discussion in the literature regarding the mechanism of action of meperidine. Formally it consists of the phenylpiperidine portion of the morphine structure, and the phenyl stereochemistry is equatorial, as expected. This stereochemistry is different from that of the phenyl ring in the phenyl-piperidine moiety of morphine, however, which is axial. Using the principles discussed in the case of acetylcholine and muscarine, it is not possible to superimpose the morphine and meperidine structures, such that both the protonated nitrogen and the phenyl rings are superimposed. A solution to this dilemma could be that the common binding site in the series is not the charged nitrogen, but the phenyl ring.[11] If only the phenyl rings are superimposed, the respective nitrogen protons of the two drugs point to a common site along the locus of points occupied by the two nitrogens, as shown. This interpretation is supported by a number of other pieces of evidence, and it serves to explain a number of inconsistencies within the series, although that discussion is not germane to this one. In the classroom, two molecules are first placed on the screen, the meperidine molecule is changed to a highlighting color and its bonds are represented by dotted lines. It is then moved with the mouse to occupy the position shown in Color Plate 6, with its hydrogen pointing directly at the hydrogen on the morphine nitrogen. Such a comparison would be very difficult, if not impossible to accomplish with skeletal models, due to steric constraints between the ring structures involved.

The following list suggests some additional, effective graphic comparisons of use in medicinal chemistry. All of the software discussed in the article is available from the author upon request.

(1) Acetylcholine vs. pilocarpine, designed to show the similarity of action of this muscarinic agonist to the natural transmitter.
(2) Epinephrine vs. clonidine, designed to show the strong similarity of clonidine to the phenethylamine neurotransmitters in their active conformations, even though the similarities are not apparent from projection formulas.
(3) Dopamine vs. chlorpromazine, designed to show one possible common mode of interaction of the neuroleptics at the dopaminergic receptor.
(4) Dopamine vs. apomorphine, designed to show the expected dopaminergic agonist action based on strong structural resemblance and substructure content.
(5) Imipramine vs. mianserin, designed to show the strong structural similarity between a classical and a nonclassical antidepressant, and to show the unique molecular shape of the tricyclic antidepressants.
(6) Spironolactone vs. aldosterone, designed to show the strong molecular similarity of an antagonist to the natural hormone.
(7) The neuromuscular blocking drugs, including *d*-tubocurarine, pancuronium and decamethonium, designed for comparison of common overlap among them.
(8) Steroid hormones, including estradiol, testosterone and progesterone, as well as the synthetic estrogen diethylstilbestrol. These substances provide a nice comparison by superimposition.
(9) The cardiotonic steroids, including digoxin, digitoxin and gitoxin, which can be compared to the sex hormones. The shapes of the two series are strikingly different when superimposed.

Enzyme active site inhibition

The third major use for microcomputer-based molecular graphics is to illustrate the mechanism of action of drugs that act as enzyme inhibitors. One example of this use is

the inhibition of dihydrofolate reductase (DHFR, EC 1.5.1.3) by methotrexate (MTX). This is an extremely well studied process, and a number of X-ray structures have been determined for MTX bound at the active site of DHFR.[9] While microprocessor-based systems are not fast enough, either graphically or computationally, to move entire enzymes smoothly and without noticeable delay, it nevertheless can be instructive to present the entire enzyme, to provide information regarding its structure and to illustrate the mechanism of its inhibition by a drug. To accomplish this, at least with the software used in this study, one needs a color projection device. Removal of the color cues used to express atom identities causes a significant loss of information in the image, because the depth cues for large molecules are diminished as well. Using a wide-angle view (Color Plate 7), the complete enzyme can be placed on the screen. The polar side-chain functional groups at the outer edge of the molecule, which provide water solubility to the enzyme, are clearly visible. By zooming in to enlarge only the active site (not shown), the van der Waals interactions that lead to the stable drug-receptor complex can be illustrated. This activity is close to the limit of what can be handled by typical microcomputer-based systems. (In fact, some would say it is beyond the limit.) There are, however, techniques one can use to speed up the computation and display processes for large structures. Hardware enhancements include increasing the clock speed of the CPU, using a memory cache and purchasing a graphics card with a wider data path. A software feature that adds efficiency to the display process is z-clipping. When both front and back z-clipping planes are active, the software does not have to draw the entire enzyme, only the active site region.

Molecular animation

Another very important topic in medicinal chemistry and biochemistry is the interaction of enzymes and receptors with their substrates and ligands, respectively. To understand the action of drugs that, for example, block an enzyme's function, one must first understand the mechanism by which the enzyme acts on its substrate. Ideally, one would like to conduct docking experiments with an enzyme and a substrate, after which the mechanistic machinery of the enzyme could transform the substrate through its transition state to product. The process could be conducted stepwise in both directions. While the docking aspect of the process is certainly feasible with large minicomputer- or workstation-based modeling systems, the transformation process is still not easily performed, even on large systems. Paradoxically, even if it were possible to carry out a process on a high-end system as described, the detail present in such an operation would be much too great for classroom use, where the essentials of the mechanism must be conveyed in a clear and unambiguous form.

We have found that the animation and presentation package GRASP[12] is of greater use in this situation than a true molecular graphics and modeling system. Using the differential animation techniques of GRASP and its accompanying graphics editor, it is straightforward to create a short animated "film clip" in cartoon form, showing the approach of the substrate to the active site, the binding and transformation in the active site, and the regeneration of the active site once the substrate has turned over. The software has a programming language and editor with which a "script" is created. Running this program either from a run-time module or from the editor plays the movie on the computer screen. Breakpoints can be built in to pause the script until a key or mouse button press occurs, so discussion can take place at intermediate points along the way. In fact, we have found that it is convenient to write the script so that the clip can be run either forward or backward from any breakpoint. This allows the instructor to replay each step in the sequence as many times as is needed so the students can reach an understanding of the enzyme function.

Figure 1 shows a selection of frames from a 189-frame animated sequence showing the function of a prototypical esterase enzyme operating on acetylcholine. In this sequence the ester is seen to bind to the active site (1a), whereupon

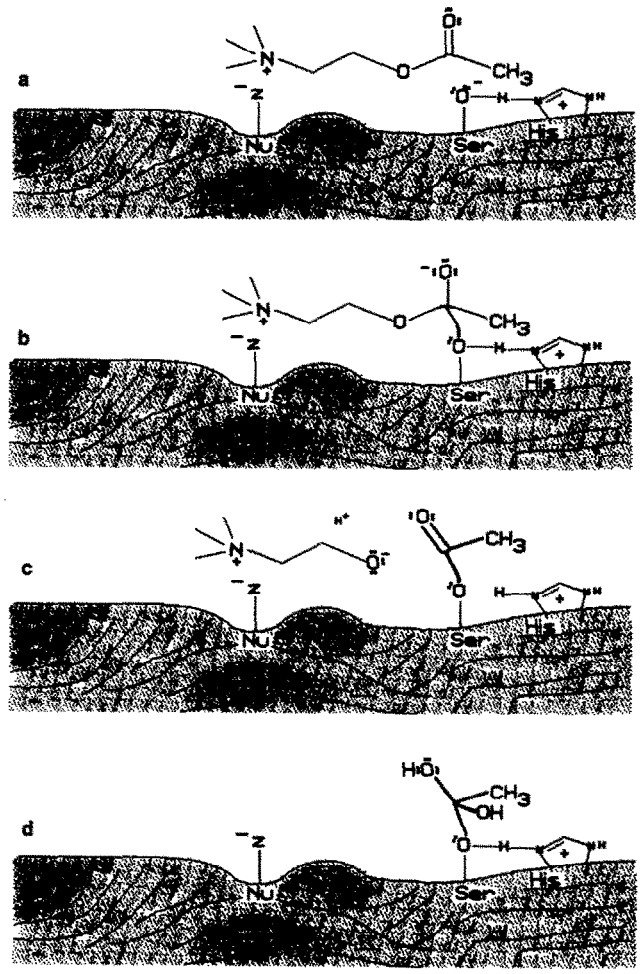

Figure 1. A representative series of frames from the molecular animation sequence showing a postulated mechanism of action of an esterase, using acetylcholine as the substrate: a, substrate bound to the active site; b, formation of the tetrahedral intermediate from attack of the serine hydroxyl; c, loss of choline and acetylation of the serine hydroxyl; and d, tetrahedral intermediate resulting from attack of water to regenerate the free serine hydroxyl group

a serine hydroxyl forms a tetrahedral covalent intermediate with the substrate (1b). Decomposition of the transition state then produces choline and an acetylated enzyme (1c). The students can see from the movie that the enzyme is temporarily inactivated during the time that the hydroxyl group is acetylated. The choline leaves the active site, then water enters and forms another covalent tetrahedral intermediate with the ester function (1d). This second intermediate breaks down to afford acetic acid, regenerating the enzyme.

A second 136-frame sequence follows (Figure 2), in which a prototype organophosphate (a known irreversible inhibitor of the enzyme) is used instead of acetylcholine. The substrate binds to the active site, forming an enzyme-inhibitor complex (2a). It then phosphorylates the serine hydroxyl (2b) with subsequent loss of fluoride ion (2c). This phosphorylated intermediate is not hydrolyzable. Instead of regenerating the enzyme as it did in the previous sequence, water approaches and only bumps into the phosphorus atom a couple of times, then leaves (2d). This indicates to the students that the enzyme is now irreversibly inactivated. Both animated sequences take less than a minute to play, but provide "living proof" of the mechanism for the students. As can be seen from the figures, the sequence is not meant to reflect scientific accuracy. Rather, it illustrates the process at the conceptual level. It is strikingly effective, nevertheless. Although the same schematic mechanism is included in the course notes in the form of a sequence of equations, the students do not gain the same appreciation of the transformation process as when it "comes alive" before their eyes.

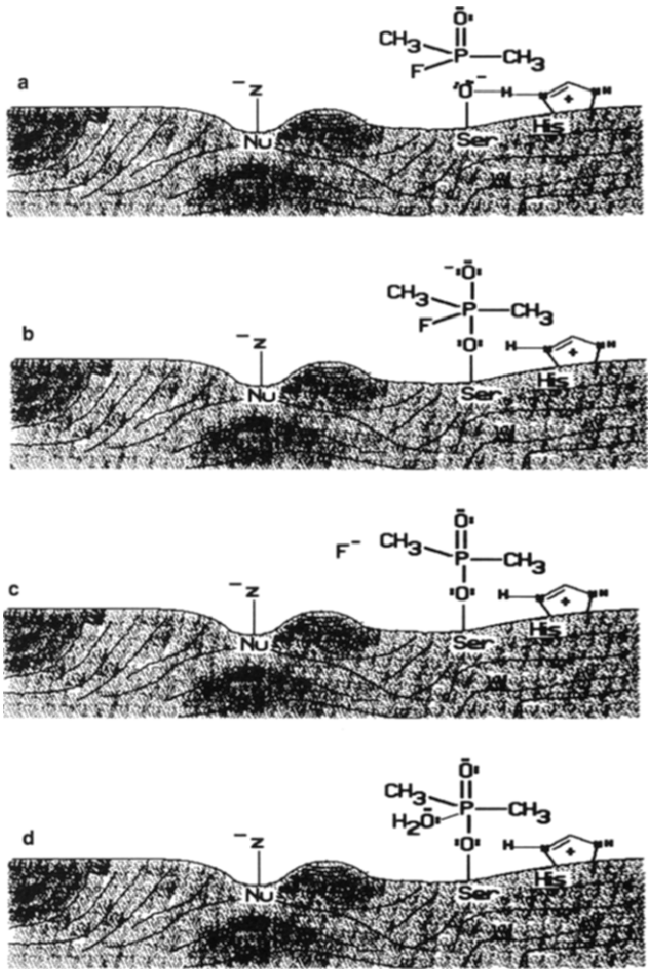

Figure 2. A representative series of frames from the molecular animation sequence showing the inhibition of an esterase, using an organophosphate: a, organophosphate–enzyme complex; b, trigonal bipyramidal intermediate formed by attack of the serine hydroxyl on the organophosphate; c, inhibited enzyme resulting from phosphorylation of the serine hydroxyl and loss of fluoride ion; and d, water shown attempting to attack the phosphate, with no success

Scripts for a number of these enzymatic processes are under development and will be made available as they are completed. Copies of the existing animation files and a GRASP run-time library are also available from me upon request. One does not need to purchase the commercial software to run scripts developed by others. Editing and further customization, however, requires a copy of the animation package.[12]

FUTURE DIRECTIONS

The techniques of classroom molecular visualization have been very well received by students, although the evidence of effectiveness of the molecular visualization techniques to date has been only anecdotal. No formal study of the effectiveness of these techniques as teaching tools has been undertaken, mainly because of the difficulty in running two sections of the same class, one using graphics techniques and the other not.

Despite the remarkable progress made in the past five years, microcomputer-based molecular visualization still is in the early stages of development. As the hardware becomes more powerful, the technology for high-resolution graphics image projection is improved, and the prices of the hardware are lowered, the quality of the modeling information available in the typical classroom will also improve.

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