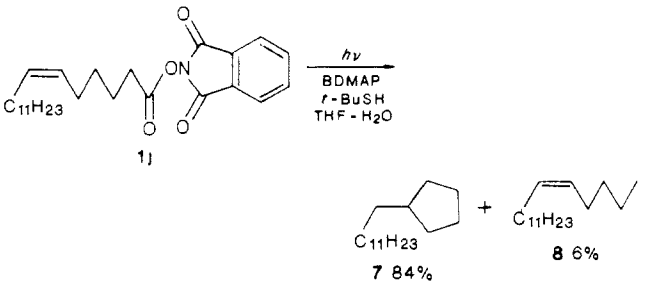

Furthermore, the present method of decarboxylation can be applied to the radical cyclization process:[21] Similar irradiation of **1j** in THF–water (95:5) in the presence of *t*-BuSH (2.2×10^{-3} M) under argon readily affords the cyclized hydrocarbon **7** (84%) accompanied by a small amount of the noncyclized hydrocarbon **8** (6%).

In summary, we have developed a new and efficient method of decarboxylation via photosensitized electron-transfer reaction initiated by visible light excitation. Further synthetic applications are in progress.

(19) *N*-(1-Naphthoyloxy)phthalimide, a typical aromatic carboxylic acid derivative, was not decarboxylated under these conditions, and 1-naphthoic acid was obtained in 71% yield.

(20) Lucchi, O. De.; Modena, G. *Tetrahedron* **1984**, *40*, 2585 and references cited therein.

(21) Curran, D. P. *Synthesis* **1988**, 417 and references cited therein.

Computer Software Reviews

MicroChem V2.5. Organic Modeling Unit. Intersoft Incorporated: One Concourse Plaza, 4711 Golf Road, Suite 412, Skokie, IL 60076. (312) 699-4143.

While DEC machines still reign supreme for molecular modeling tasks, useful microcomputer packages have been available in the IBM world for several years. Though the graphics interface of the Macintosh seems ideal for interactions between the structural chemist and computer, and Mac-based molecular drawing programs are the generally acknowledged leaders in the field, real molecular modeling for the Mac has been slow in appearing as a result of the lack of a floating-point coprocessor on the Mac Plus and SE.

Even without coprocessor support, the low end Macs are powerful graphics machines, and the first entry in the race to provide Mac-equipped chemists with desktop chemical modeling tools has appeared. While limited in scope, MicroChem Version 2.5 runs on the Mac Plus, SE and II—all in black and white. The entire set of MicroChem applications includes Organic, Inorganic (zeolites), Macromolecular (nonbiological polymers), and Drug Design (Group Additivity Properties) Modules. All of these modules use the same program to display 3-D structures. This review deals only with the Organic Modeling Unit.

MicroChem Organic comes on a single floppy that is not copy protected. Installation on a hard disk is, of course, trivial. Presumably in order to allow operation on 1Mb machines, MicroChem Organic is broken into six (yes 6!) separate applications. Without a RAM upgrade and MultiFinder, be prepared to launch and quit a lot.

The applications are the following: InputMol; BuildMol; AssembleMol; DisplayMol; TwistMol; and FormatMol. Together these applications require only 485 Kb of disk space. Also required are several data files, totaling only 22 Kb. Finally, a library of 32 predrawn structures, weighing in at 73 Kb, is included. MicroChem V2.5 runs fine on a stock Mac Plus with two 800K floppy drives.

FormatMol is a small utility designed to allow translation of data between several different formats. According to the documentation, MicroChem uses the Chemlab-II format, and can translate and write files in molfile (MDL), Sybyl (Tripos), and a version of the CSSR (Cambridge Crystallographic Database) formats. The latter is compatible with Chem-X (Chemical Design Ltd.). I did not test these utilities, but MicroChem molecule files are simply text files that can be opened and edited with MS Word. Undoubtedly, a knowledgable computational chemist would have minimal trouble inputing and exporting data between MicroChem and, e.g., a VAX-based program.

The five remaining applications perform three basic functions. InputMol, BuildMol, and AssembleMol allow the creation of 3-D molecular structures; DisplayMol allows examination of the structures and modification of the structures by rotation about acyclic bonds; and TwistMol allows calculation of conformational strain energies. Together, the package provides powerful tools for creation of presentation graphics and for examination of structures—with many frustrating limitations and quirks.

A brief description of the operation of each application is given here, followed by a summary of the performance of the package as a whole. Most of the testing was done using an 8 Mb Mac II, though all functions also operated as advertised on a 1 Mb floppy-based Mac Plus.

Assuming a MicroChem-readable 3-D molecule file is unavailable, InputMol affords basic tools for drawing structures into MicroChem. Using the drawing tools is quite simple, though somewhat awkward relative to molecular drawing approaches available in other Mac applications such as ChemDraw and Chemintosh. Even so, it is very simple to construct 2-D structural formulas containing most of the atoms (including silicon and aluminum) and "types" (e.g. sp^3, aromatic, cation) normally encountered by organic chemists. These formulas may then be converted to 3-D structures in one of two ways. First, each atom of a 2-D formula drawn on the active screen (called the "benchtop") may be tagged with fractional coordinates. Then, entry of unit cell dimensions and angles from a crystal structure affords a 3-D molecule. Cartesian coordinates may also be used. The resulting structures may then be viewed with DisplayMol as described below, or modified to produce new structures.

In general, of course, coordinates are not available. In this case, the 2-D formula is saved, and BuildMol is used to create an idealized 3-D structure. For acyclic fragments, BuildMol simply generates a geometrically correct structure based upon simple bond length and bond angle rules. The conformation that results is fairly random, but it depends to a large extent upon the 2-D input. No minimization occurs during this process. Cyclic fragments, on the other hand, are handled with a "conjugate gradients" method to minimize deviations from the preferred equilibrium bond angles and lengths. When a formula is opened from BuildMol, hydrogen atoms are automatically added in idealized positions. This allows the easy creation of crystal structures with H-atoms if coordinates for the hydrogens are not available by simply opening a crystal structure created with InputMol. When a 2-D formula is opened with BuildMol, a nonsense structure appears—waiting to be transformed into a 3-D molecular model. Choosing "Make 3-D Structure" from a menu then starts the process of model building.

It is possible to define the level of convergence required before BuildMol stops the process, and also to set a time limit on the calculation. Visual feedback is provided to indicate how close to convergence the program is while it is working. Acyclic fragments converge on an idealized structure quite rapidly. However, for ring compounds, be prepared to wait. While, e.g., cyclohexane converges very quickly, I found that fused ring systems are surprisingly slow to converge. For example, building a "3-D" model of phenanthroline on a Mac II took over an hour with use of the default "convergence parameter". Given that the default time limit set for building 3-D models is *24 hours*, one must be patient. The manual states that this default time limit "is sufficient for most molecules". It is true, however, that often the structure comes close to convergence, and the program spends considerable time tweaking. A graph showing the degree of convergence is, as mentioned above, displayed during the calculations. If one gets tired of waiting, it is possible to stop the program at any time, affording the 3-D structure present in memory at that time. In my experience, this often gives a perfectly adequate model for many applications.

Starting with a flat hexagon, I obtained a chair cyclohexane conformation after running BuildMol. The conformation obtained for acyclic fragments seems arbitrary. Boat cyclohexanes and specific ring fusion stereochemistry in saturated fused-ring systems may be obtained relatively easily with use of a feature present in InputMol. Specifically, InputMol allows each *ring* atom to be tagged with a "stereochemical" descriptor: front; plane; or back. Once an atom is tagged in InputMol, a visual cue (bold for "front", gray for "back") appears showing where

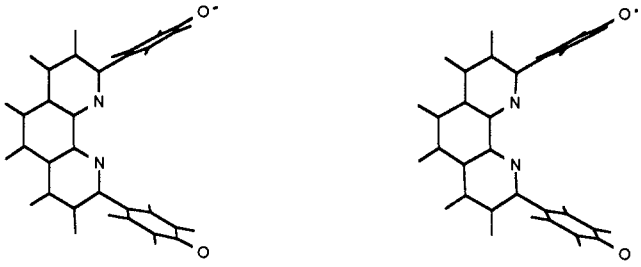

Figure 1. A stereoview of diphenylphenanthroline diphenol.

that atom is relative to the plane of the screen. These tags do not apply to acyclic atoms—absolute and relative stereochemistry is in general arbitrarily set by BuildMol, but it can be changed as described below. When the modified 2-D structure is "idealized" by BuildMol, some control over ring conformation and relative stereochemistry at ring fusions is achieved. Thus, it was possible to create cis and trans decalines with any combination of boat and chair rings. However, since the ring minimizer uses only bond length and angle data, I found it impossible to create a twist-boat using BuildMol. Indeed, since bond rotations in TwistMol and DisplayMol only apply to acyclic bonds, I think it is impossible to obtain a twist-boat with MicroChem without 3-D coordinates.

Given the long times required to converge on idealized ring structures, it is not surprising that MicroChem V2.5 includes a utility for creating new molecules from 3-D structural fragments. AssembleMol allows the connection of any two fragments to create a new molecule. The fragments can only be connected by one bond—AssembleMol cannot be used to fuse rings. Even so, this utility is *extremely* useful and important. Using the library of structures included with MicroChem, and with a library of ones own favorites, complicated molecules can be created much more quickly with AssembleMol than by starting from scratch with a 2-D drawing in InputMol, followed by a minimization in BuildMol. Fragments are joined by simply specifying one "terminal" atom (H or halogen) on each fragment and selecting "Connect" from a menu. This process is very fast. For example, creation of diphenylphenanthroline diphenol (see below) starting with phenol and phenanthroline was very fast and simple. Also, aside from allowing connection of structural fragments, AssembleMol contains a utility for converting a model to its enantiomer, and for inverting the configuration at a carbon. For example, selecting the "Invert" command and then clicking on the methyl group and C-1 hydrogen atom of methylcyclohexane converts the equatorial conformation to the axial conformation, and vice-versa. Clicking on the chlorine atom and C-2 hydrogen of 2-chlorobutane converts the *R* enantiomer to the *S* enantiomer. This is important since it is not possible to set absolute configuration in InputMol or BuildMol.

Once a 3-D model is built, DisplayMol is used to adjust acyclic conformations, examine the model, and create very nice presentation graphics. A 3-D structure may be viewed as a simple framework model without labels. This option affords the fastest rotations. Alternatively, heteroatoms may be labeled by element with the conventional lettering scheme, all atoms may be labeled according to element, or according to atom type (a code used by MicroChem to label, e.g., sp^3, sp^2, and aromatic carbons), or atom number (according to the order the atoms were entered into the structure). The labeled or unlabeled framework model may be viewed as a stereo pair. A utility for defining the separation of the two views is provided. The separation may be set to a negative value, allowing chemists such as myself, who view stereo pairs with crossed eyes, to see the correct enantiomer. Finally, a ball-and-stick representation, or space-filling model, can be viewed. These models are shown in mono only.

Any model open in DisplayMol can be copied to the clipboard for importation into another Mac application. Models come through as vector images (not bit maps). Thus, when pasted into MacDrawn, each element of a framework model (lines and lettering) is individually selectable and editable. The atoms of space filling models come from the clipboard as individual circles that may be selected and defined with regard to pattern. When a space filling model is pasted into MacDraw II on a color Mac II, several colors appear in the pattern menu, and the atoms are colored—carbons are red, hydrogens white, and all other atoms a shade of red. Each atom may be selected and colored according to the users preference. While the atoms are "flat" (i.e., not shaded), beautiful color images of space filling models or ball and stick models can be obtained with MacDraw II. The figures given here show a framework stereoview, ball and stick model, and spacefilling model of diphenylphenanthroline diphenol pasted directly from the clipboard into Microsoft Word.

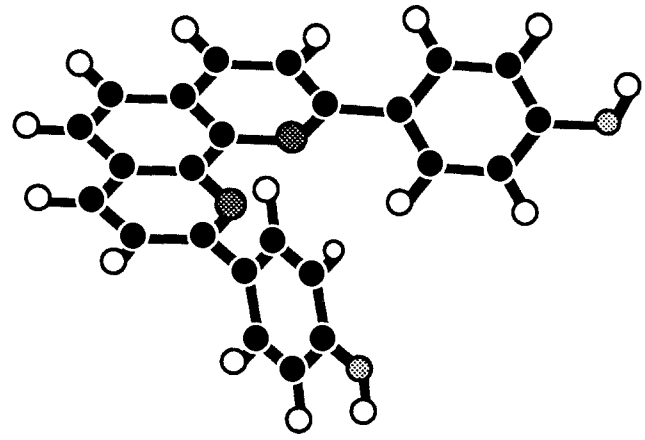

Figure 2. A different view of diphenylphenanthroline diphenol as a ball and stick model.

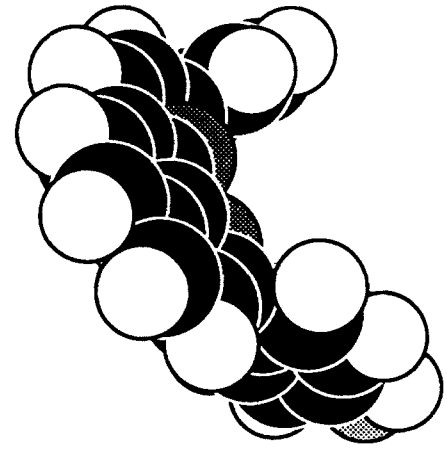

Figure 3. A third view of diphenylphenanthroline diphenol as a space filling model.

As can be seen by examining these graphics, each represents a different view of the molecule. This is accomplished by using the rotation tools in MicroChem. Of course, you may rotate about the *X*, *Y*, and *Z* axes of your molecule. MicroChem uses the geometric center of the molecule as the origin, but you may define any atom in the structure as the "center" of the molecule for the rotations. The entire process of generating the graphics shown in the Figures (after the 3-D model had been built!), pasting them into Word and labeling them, took less than 1 min with all five MicroChem applications, Word and MacDraw II running on the 8 Mb Mac II under MultiFinder.

In addition to rotation of the entire molecule, it is possible to rotate about any acyclic bond. For example, AssembleMol set the phenol rings coplanar with the phenanthroline unit when the model was first created. Using the bond rotation tool in DisplayMol easily allowed creation of the more realistic model shown in the figures. DisplayMol also has several additional powerful tools for examining models. A Newman Projection tool generates a nice view down any bond. Also, a useful "sight" command, somewhat similar to the Newman Projection, allows orientation of the molecule by clicking on any three atoms. The first two atoms are oriented along *Z*, and the third atom is oriented along *Y*. Bond angles, lengths, dihedral angles, and distances between atoms may be measured by using simple point and click techniques. The magnification and perspective of the models can be adjusted. The drawing in Figure 4 was created easily with these tools.

Finally, DisplayMol has an animation tool that allows "movies" of rotating molecules to be displayed on screen. The movie may simply show the entire molecule rotating about an axis, or the movie can display rotation about one bond, or several bonds rotating in concert. For example a neat (though not particularly useful) movie of the diphenylphenanthroline diphenol molecule with both phenol rings rotating together was easy to generate. The speed of rotation of the moves can be adjusted, but the frames change in 30° increments, which I found a bit choppy.

The final application in the MicroChem suite allows some force field calculations to be applied to models. TwistMol is also the largest in terms of code size. It is important to note that TwistMol *does not* allow

Figure 4. Another view of our model with perspective turned to maximum and magnification set to 200% (300% is the maximum magnification allowed). The drawing was reduced to 50% after pasting into Word.

minimization. The only minimizer in MicroChem is the ring-creating facility in BuildMol. TwistMol does, however, calculate steric and electrostatic strain energy for any conformation input into the application. The Del Re method is used to estimate partial charges on the atoms, or you can supply your own charges. TwistMol *does not* allow any changes of bond lengths or angles from within the application.

What TwistMol does allow, however, is a "fixed valence" molecular mechanics calculation, where energies are computed for rotamers generated by rotation about single bonds. Thus, one may select a bond, an arc (e.g. from 0° to 180°), and an increment (e.g. 10°), and let TwistMol generate a family of rotamers, and calculate the strain energy for each. After completion of the calculation, the lowest energy conformation is displayed, and all of the data generated in the calculation are stored in a text file. As many as 10 bonds may be selected in this process to generate an array of conformations that are screened in one batch process. Scanning rotamers about one bond is fairly quick (a 0°–180° scan in 10° increments on one of the Ar–Ar single bonds in our model took a little over 1 min on the Mac II). However, naturally the more bonds selected, the longer the process takes. Patience here is necessary. In the manual, it is stated that torsional parameters will be included in future versions, but the version reviewed did not include any torsional strain in the calculations.

While clearly very interesting, I am not sure how useful TwistMol will really be. The fixed valence approach for scanning rotamers only provides a very approximate picture of the conformational surface of a molecule. For example, scanning *n*-butane in 10° increments about the C2–C3 bond gave the anti conformation as the minimum. However, the conformation with a dihedral angle of 90° was only 0.01 kcal/mol higher in energy according to the calculation. For the axial and equatorial methylcyclohexanes, even with a scan in 10° increments about the C1–methyl bond, the axial conformer came out more than 5 kcal/mol above the equatorial conformer.

Upon completion of a scan, TwistMol puts the data obtained from the scan in a text file. Opening this file with a word processor allows a quick perusal of the conformations and strain energies obtained in the scan. Unfortunately, due to the way MicroChem delimits columns and presents the data, I was not able to devise a simple way to get the data into a spreadsheet or plotting program to plot the surface. The manual states that future versions will include a plotting facility.

Finally, TwistMol includes a utility affording some control over ring conformations. Thus, starting with chair cyclohexane, selecting the "pucker" command, and then clicking on one of the carbons of the chair affords a boat. I cannot comment on the general availability of this option, however, since with any decalins, every time I tried the pucker command, a message appeared stating something to the effect that MicroChem could not change the pucker of that carbon. As described above, InputMol allows some control of ring conformation with the stereochemistry option.

Overall, the MicroChem Organic Module provided some very useful tools. I was able to easily input crystal coordinates into my Mac and examine a 3-D model of the crystal structure in stereo. This, with the Newman projection option, made construction of a Dreidling model of the structure trivial. Of course, the same features are available on other Mac applications at a lower cost (e.g. Ball&Stick). However, with MicroChem I could then modify my structure by rotating about acyclic bonds, perform some simple energy calculations, and get very nice looking presentation graphics for inclusion in a proposal or publication.

That is the good news. Unfortunately, I found the limitations and quirks of the program to be bothersome. While the limitation on the number of atoms (500) did not present a problem for me, I was frustrated by the lack of support for displaying more than one molecule on the benchtop at one time. Thus, it is not possible to create complexes or perform even rudamentary modelling of "docking" processes. For presentation graphics, this problem can be circumvented somewhat by using a vector drawing program (e.g. MacDraw II). Since the models transfer as vector images, it is quite simple to "eclipse" parts of one molecule with another to create non-covalent complexes.

Finally, in my view MicroChem affords a very poor implementation of the Mac interface. Most glaringly, the method used for rotations was actually *worse* than the typical IBM-style command-oriented approach. In order to rotate about a given axis or bond, a command (e.g. Rotate X) is selected from a menu. This brings up a dialog box at the bottom of the screen with a scroll bar and number indicating the rotation in degrees. Clicking on the arrows changes the rotation in 1° increments, but on the Mac II scrolling is so fast it was almost impossible to stop at a specific number. Clicking on either side of the box in the scroll bar changed the number in 5° increments. After hitting the value of the rotation I wanted, it was necessary to then select "Redraw" from a menu to obtain the rotated structure.

Incredibly, while rotation is possible in all applications but BuildMol, it is implemented in at least three different ways. The Rotate and Redraw commands sometimes appear in the same menu, and sometimes in different menus. A partial saving grace is that *every* command in every application has a Command-key equivalent. In all modules supporting rotation, Command-j, Command-k, and Command-l do not open the dialog box, but rather perform a 30° rotation about the *X*, *Y*, and *Z* axes, respectively. Thus it is possible to be looking at a 3-D stereoview and rotate from the keyboard somewhat interactively. Holding the Command-key down continues the rotation, a bit more slowly than the animation facility in DisplayMol, but similar. This Command-key rotation facility, in my view, saves the program from being unusable, though it would be great to be able to change the default rotation increment from 30°, which is a bit too large.

Naturally, it is often desirable to reverse the direction of the rotations. According to the manual, this is done in a standard Mac fashion by using the Option-Command-key combination. However, in my version of the program, this approach did not work. Instead, Shift-Command-key reversed the direction of the rotation—but every time! Thus, in order to reverse rotation directions, it was necessary to use the Shift key *only once*. Command-key strokes then continued rotating in that direction until the Shift key was used again. Another example of deviation from the standard Mac interface is the method of stopping a minimization in BuildMol. The standard Mac method would be Command-period. In MicroChem, one clicks the cursor in a bar on the right of the screen, where the scroll bar would normally be, to stop the calculation.

This may sound like nit-picking. But, Mac users expect an intuitive, innovative interface. To find such a cumbersome approach to 3-D rotation on the Mac was very dissappointing. Also, the version I reviewed seemed loaded with glitches and bugs. For example, often rotation of space filling models would show nonsense at certain views. This was even true for benzene, where the carbons seemed to jump out of the ring in some views. In AssembleMol, when using the "invert" command to change axial to equatorial substuents, choosing "Save As" from the "File" menu *overwrites* the original file on disk, while choosing "save" brings up a dialog box for renaming the file. Be careful of this one! Finally, on the Mac II under MultiFinder, a system crash was guaranteed during a long session, though the time between crashes was long enough that useful work could certainly be accomplished.

In summary, given that MicroChem is really the only game in town right now, and that upgrades are promised in the future, I feel that many chemists equipped with Macs will find the program very useful. Also, the manual advertises a Mac II-specific version called MicroChem/XP, which takes advantage of the 68881 coprocessor and announces a color version coming soon. With some improvements in the interface, and true minimization capabilities, MicroChem could become a truly outstanding tool for professional chemists.

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