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a)

b)

Figure 2. Enlarged section of the correlation region for H-ε and H-ζ protons of the MeBmt residue[11] (a) before and (b) after appropriate data handling. For all the figures, the same positive and negative contour levels were plotted without discrimination. All data processing was accomplished by the NMR2 software (New Methods Research, Inc., Syracuse, NY).

comparison with other methods. The essential step is selective removal of the 90° out-of-phase diagonal peaks from the familiar pure-phase two-dimensional spectrum through simple data processing maneuvers. It can be accomplished by successive absorptive–dispersive phase setting, deletion of unwanted signals, and reconstruction of imaginaries by Hilbert transformation[9] for

rephasing. This approach minimizes the necessary number of scans to one in the ultimate case,[10] when sign discrimination is achieved by setting the carrier at one end of the region of interest. The data processing procedure includes the following major steps: phasing the diagonal peaks to pure absorption in both dimensions, removal (or, alternatively, scaling) of the diagonal, replacement of imaginary data using Hilbert transformation, and rephasing in both dimensions by 90°. All this is straightforward to automate if simple autophase routines are provided. The ultimately simple experimental setup and automated computation make the overall procedure extremely user-friendly.

As an example, applying this strategy in two dimensions, the S.COSY spectrum of cyclosporin A[11] is shown (Figure 1). The presented data were previously acquired as the measured 2D counterpart for a P.COSY experiment. All the information involved in a pure-phase spectrum is retained. Cross peaks, even very close to the diagonal, are well seen and easy to analyze (Figure 2).

In conclusion, an ultimately simple and easy to automate overall procedure (SIMPLE-COSY) has been developed for acquisition and data processing of *J*-correlation spectra. In the presented approach, only a single dataset needs to be acquired, which is processed by using successive absorption–dispersion phasing, removing the diagonal, and rephasing data by the help of Hilbert transformation. The strategy is applicable in more than two dimensions, too, and could be useful in all cases when diagonal and cross peaks have a uniform phase difference.

Note Added in Proof. Recently a closely related approach has been published (Tsang, P.; Wright, P. E.; Rance, M. *J. Magn. Reson.* **1990**, *88*, 210), focusing on 1D applications.

(9) Ernst, R. R. *J. Magn. Reson.* **1969**, *1*, 7.
(10) Marion, D.; Ikura, M.; Tschudin, R.; Bax, A. *J. Magn. Reson.* **1989**, *85*, 393.
(11) Kessler, H.; Loosli, H.-R.; Oschkinat, H. *Helv. Chim. Acta* **1985**, *68*, 661.

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Alchemy II for Macintosh. Version 1.00. Tripos Associates Inc.: 1699 S. Hanley Road, Suite 303, St. Louis, MO 63144. List price $950.00; educational discounted price $650.00.

At long last, action on the Macintosh molecular modeling front is heating up, and several very useful packages have recently become available. These include Chem3D Plus from Cambridge Scientific Computing, PC Model for the Macintosh from Serina Software, Microchem by Anthony Hopfinger (University of Illinois at Chicago), and the subject of this review, Alchemy II from Tripos Associates. A recent review of Alchemy II published in MacWorld (Charles Seiter, MacWorld, October 1990 issue, p 235) provides a brief comparison of the capabilities of Alchemy II and Chem3D (the latter includes "MM2 with pi-electron calculation and a basic molecular dynamics capability").

This review focuses upon the capabilities and limitations|of Alchemy II for Macintosh, which requires an 8-bit color Mac system with a minimum of 2 Mb of RAM (the review was done using a Mac II with 8 Mb of RAM, and giving Alchemy II a 1Mb MultiFinder partition, System 6.0.5, and 32 bit quickdraw installed). In brief, this is a very stable, professional program, which would be highly useful for practicing lab chemists and educators. It sports an interesting, very easy to use 3D drawing interface, a minimizer for obtaining reasonable conformations, and outstanding, essentially real time rotation and translation of color

framework models. It also provides very nice color space-filling models and ball-and-stick models at a useful speed, though far from real time (converting a DNA duplex framework model to an 8-bit shaded color graphic such as those used to create the half-tones presented below took about 6 s).

Aside from the excellent features mentioned above, Alchemy II provides the following.

The manual is concise, informative, and very well written. It gives an especially good account of the force field method and provides all the information necessary for creation of custom atom types and parameters. The minimizer included with the program is not the standard MM2, but rather the proprietary Tripos force field. This force field seemed quite useful to me, giving very reasonable minima and strain energies for standard molecules and showing better than VAX 11-780 speeds on the 16-MHz Mac II. There is no capability, however, for dealing with charges, or for minimizing intermolecular interactions. Thus, while one may display many molecules on the screen, it is only possible to minimize one at a time, and the energy obtained is that for the isolated molecule. While it is possible to monitor six interatomic distances for atom pairs in separate molecules in real time during rotation or translation of one of the molecules, I found this approach to "docking" to be very cumbersome.

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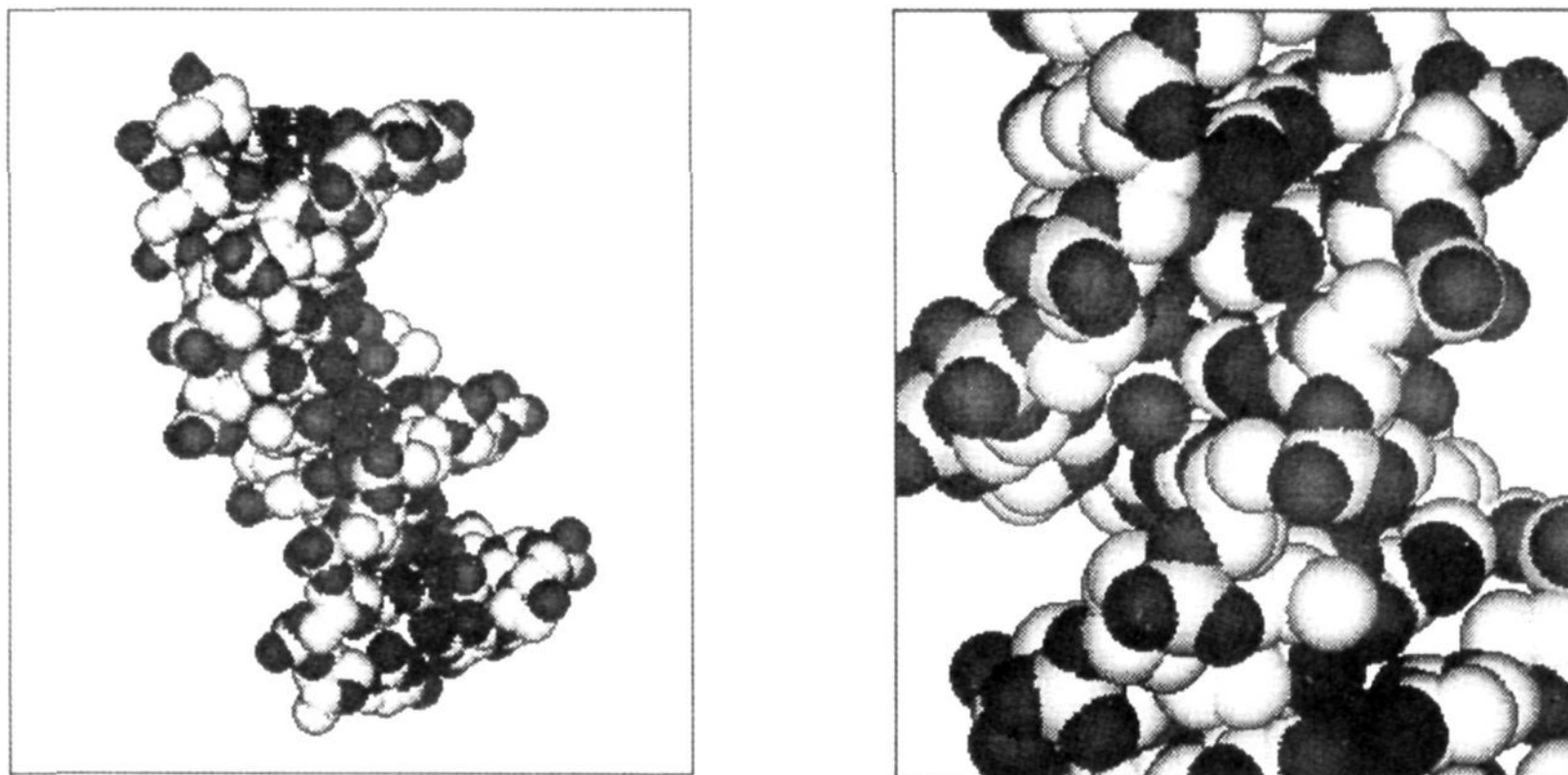
Figure 1. Two frames of a 50 frame "rotating and zooming" animation created with Alchemy II, flash-it and Image 1.22. The two PICT files were placed directly into PageMaker and printed with a Laserwriter II NT. H atoms are suppressed.

The program reads and writes its own molecule and molecule fragment files, plus Sybyl files, MM2 files, and crystallographic fractional coordinate files. By using Sybyl-formatted files, it was easy to get Alchemy structures in and out of MicroChem and MacModel (the excellent but unsupported program from Scott Kahn, University of Illinois at Urbana—Champaign).

A powerful "fitting" module, which allows fast, quantitative comparison of two different structures, is provided. Entire molecules or molecule fragments may be compared. In addition, the capability of viewing framework, ball-and-stick, or spacefilling models in stereo (stereopairs may be displayed as either "relaxed" or "cross-eyed" views) affords a useful alternative to true 3-D perspective for viewing models. The stereopairs in combination with the 3-D drawing tool or a useful "twist" command which allows interactive modification of up to six dihedrals using point and click techniques made it quite easy to obtain reasonable conformations before minimization.

I liked the Alchemy II capability of automatically labeling stereocenters following the CIP rules. The program did, however, give incorrect answers for the two *meso*-2,3,4-trichloropentane isomers, ignoring the stereogenic center at carbon 3 (the infamous "pseudo-chiral center").

The program's interface did suffer from some fairly minor negative features. Thus, there is no "lasso" or "selection marque" capability, so it is not possible to select parts of molecules conveniently. For example, in order to obtain a molecule fragment from a large molecular structure, it is necessary to select "delete atom" from the menu, then shift-click the atoms to delete one at a time. Also there are no keyboard equivalents built into the menus. Far more problematical, the Undo command seems totally disabled!

Another somewhat annoying problem is that there are not enough colors. Thus, F, Cl, and Br are all the same color! Also, the molecule measurement capabilities are just adequate. Thus, one can measure distances, angles, and torsion angles. But, it is not possible to compute centroids, create planes, and measure distances relative to the centroids or planes. These features, included in MacModel, are very useful. A more serious problem with Alchemy II is that there is no way to automate minimization of many starting configurations (no automated dihedral drivers).

Finally, for typical Macintosh users I suspect the biggest problem with Alchemy II would be the very limited print capabilities with a Laserwriter. Alchemy II can save any graphics as PICT files and can save framework models as PICTs or HPGL files. The latter are useful for standard plotter-equipped setups. But, the PICT files created from space-filling models are flat-color PICT objects (i.e. not the nice shaded graphics you see on the Alchemy screen) composed of many ungrouped lines, so they cannot be edited by using fill patterns in MacDraw II, for example, as can the flat-color space-filling models created with MicroChem, and look very poor when printed. The same poor graphics are obtained when an Alchemy space-filling model is copied to the clipboard then pasted into Microsoft Word 4.0, PageMaker, or an 8-bit color paint program.

It is, of course, very frustrating to have beautiful shaded graphics on the screen and not be able to edit or manipulate them in another Mac application, and this would be a serious limitation of Alchemy II except that any of the many Mac color screen-shot applications (color versions of the standard Mac "command-shift-3" FKEY) save the situation. Thus, by using the excellent share-ware program flash-it (on CompuServe, available for downloading in the MacPro DAs/FKEYs/INITs library as FLSHT1.SIT, requires stuffit or unstuffit to de-compress), it was easy to save shaded color spacefilling models as 8-bit PICT files and then place them into PageMaker documents or open them with color paint programs for editing or embellishment. Indeed, the PageMaker print driver created quite adequate half-tone output of such graphics when printed with a Laserwriter II NT (see Figure 1).

The ability to save Alchemy II screens as 8-bit PICT files also alleviates another short coming of the program—lack of a facility for creating animated (e.g. rotating) spacefilling models. By using flash-it in combination with the freeware 8-bit color image processing program Image (developed in the NIH by Wayne Rasband and also available on CompuServe or America Online) it was possible to create a very nice 50-frame animation of the DNA model shown in the figure by "shooting" Alchemy II "frames" with flash-it and then running the frames with the Image "run movie" command. At 30 frames/s, the animation looked great, though with PICTs as complicated as these, only a few seconds of animation can be loaded using a 5 Mb MultiFinder partition for Image.

One advantage of this modular approach to molecule animation is that the animator has complete control over the frames. Thus, instead of merely rotating the DNA molecule, it was easy to rotate *and* zoom in, to give effects somewhat reminiscent of Luke Skywalker attacking the Imperial Death Star. By using Alchemy II in combination with a screen shot and animation program and some of the recently released video hardware now available for the Mac for under $3000, it would be a relatively simple matter to create long full-motion molecule animations on video tape.

In the process of manipulating Alchemy II images under MultiFinder, another annoying feature of the program came to light, however. Thus, for some reason Alchemy II uses different color lookup tables (CLUTs) for framework models and for spacefilling models. Also, the program seems to define the CLUT of every open application under MultiFinder. Thus, strange things happen to a spacefilling model in Image when Alchemy is set on the framework model view, to which it defaults every time it is made active.

Even given the caveats, I found Alchemy II a highly useful program. With the Tripos force field, and several interesting bells and whistles, this serious molecular modeling application definitely deserves a look from Mac-prone chemists.

The vendor indicates that the PICT file problems and the color lookup table conflicts have been corrected in the latest version of Alchemy II.

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