Application Note

Teaching 2D NMR Spectroscopy Using Software Tools

ACD/2D NMR Predictor

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Introduction

One of the emerging analytical techniques being used more and more in the pharmaceutical and chemical industries is 2D NMR Spectroscopy. While the teaching of 1D NMR Spectroscopy has become mandatory in the majority of the chemistry departments around the world, many students are only learning the bare minimum of 2D NMR interpretation while some are not even getting a proper introduction until graduate school for reasons of instrument limitations or inexperience within the faculty.

In order to fully prepare students for future jobs in industry, it is important for teachers and professors to educate their students about 2D NMR. Unfortunately, 2D NMR is not a trivial concept and can be a very hard subject to understand. In order to give students a strong introduction in 2D NMR without taking up too much time teaching it or producing the spectra, software tools can be used to help professors simulate different 2D NMR experiments, provide visual aids, and quickly create different assignments and examinations. The purpose of this application note is to outline how ACD/2D NMR Predictor can help instructors create dynamic lectures and challenging assignments and examinations.

Simulating a 2D NMR Experiment in the Classroom

Unfortunately, some academic institutions may not have an NMR instrument that is capable of acquiring 2D NMR experiments. In some instances, there may be no time to acquire a 2D NMR experiment prior to a lesson. With ACD/2D NMR Predictor, an actual 2D NMR experiment can be replaced with a simulated 2D NMR spectrum based on a chemical structure. By simply drawing a chemical structure in ACD/ChemSketch, the user can simulate any number of 2D NMR experiments. In addition, the user can avoid spending the time drawing a chemical structure and simply copy and paste a structure from the ACD/Dictionary (Figure 1). In this example, the chemical structure for Ramipril is found in the Dictionary by typing in the common name, and then pasted into ChemSketch. Figure 2 shows the result of a simulated H-H COSY experiment that can be generated from the chemical structure in a matter of seconds.

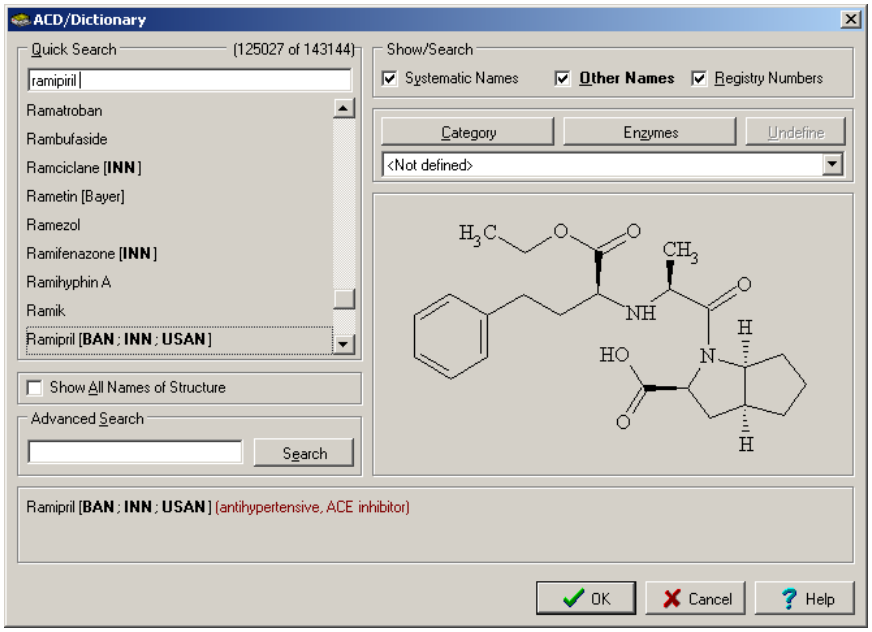

Figure 1. *ACD/Dictionary (included with ACD/2D NMR Predictor) contains over 143,000 published chemical* structures that can be searched, and copy and pasted into the ChemSketch interface.

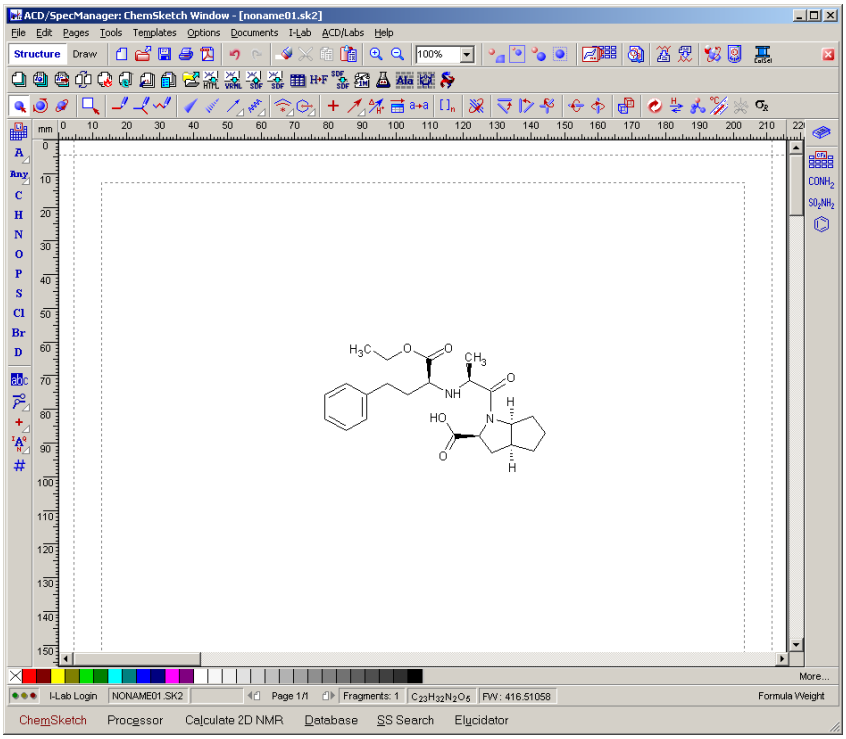

Figure 2. *Once pasted into the ACD/ChemSketch interface, a 2D NMR spectrum can be predicted based on the chemical structure of Ramipril.*

The connectivity between the chemical structure and the correlations in the calculated spectrum allow the user to easily identify which atoms in the structure are responsible for the correlations in the spectrum. In this particular example, the correlation at 2.47 and 1.64 ppm is responsible for the ^{3}J coupling between proton 3a and proton 4 (Figure 3). The interface provides an interactive platform to illustrate the structural assignments of a 2D NMR spectrum. In addition, different regions of the 2D NMR spectrum can be zoomed in on to get a better view of the correlations (Figure 4).

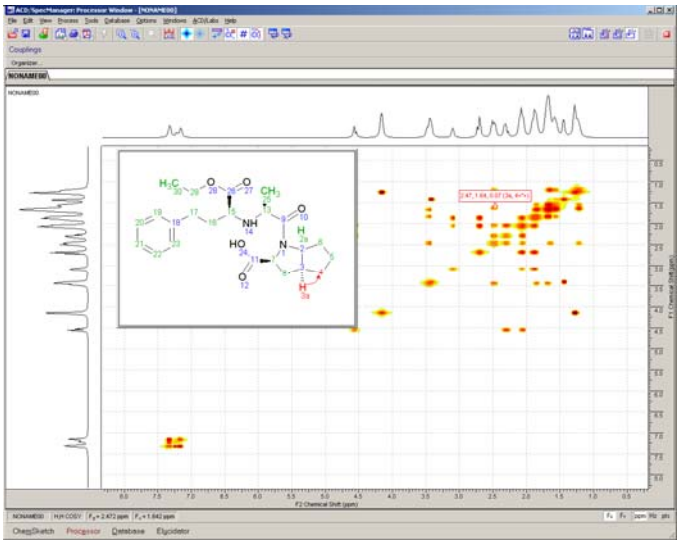

Figure 3. *A simulated H,H COSY of Ramipril. By placing the cursor over a correlation, the relevant atoms are highlighted in the chemical structure.*

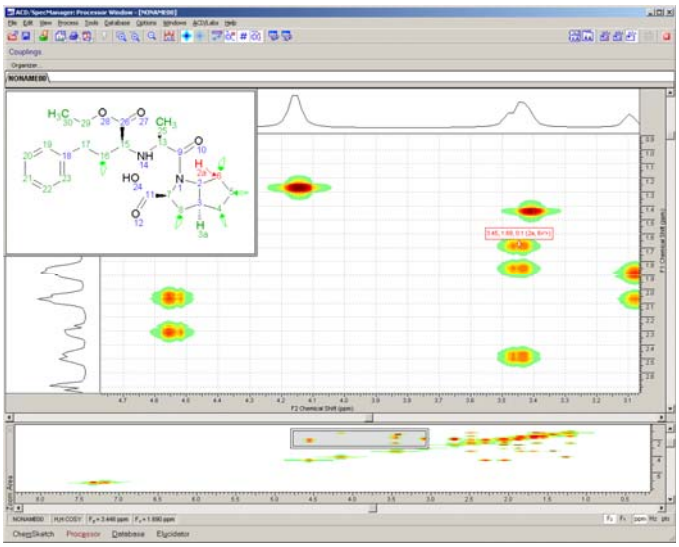

Figure 4. *Zoomed in region of the H,H COSY spectrum of Ramipril.*

Furthermore, following a prediction, the software automatically generates correlation arrows that reveal the different types of couplings that are being observed in the spectrum. The software differentiates these correlation arrows by color depending on the J-values. The arrows can also be toggled on and off for easy viewing (Figure 5).

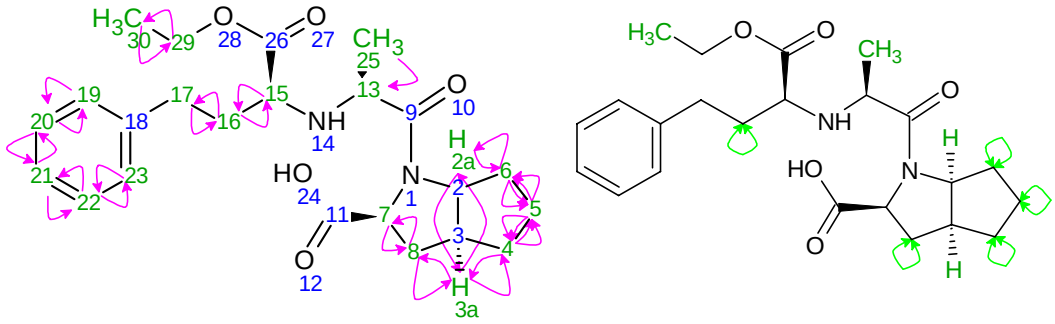

Figure 5. *Following a prediction, correlation arrows are automatically generated on the chemical structure. Some of the observed ^{2}J (Green) and ^{3}J (Pink) correlations from the simulated H,H COSY of Ramipril are highlighted in the chemical structure.*

Designing Assignment and Examination Templates

The reporting capabilities in ACD/2D NMR Predictor provide a fast and easy way to create assignment and examination templates. Once the templates are customized to meet the user's needs, new assignments and examinations can be created in seconds. Following an NMR prediction, users can update their examination templates with new chemical structures, 2D NMR spectra, etc. Figures 6 and 7 illustrate a couple of sample examination templates that allow the user to input different chemical structures and NMR spectra from the 2D NMR prediction window at the click of a button. By combining these templates with the depth of ACD/Dictionary, professors will never have to use the same examples for more than one exam ever again!

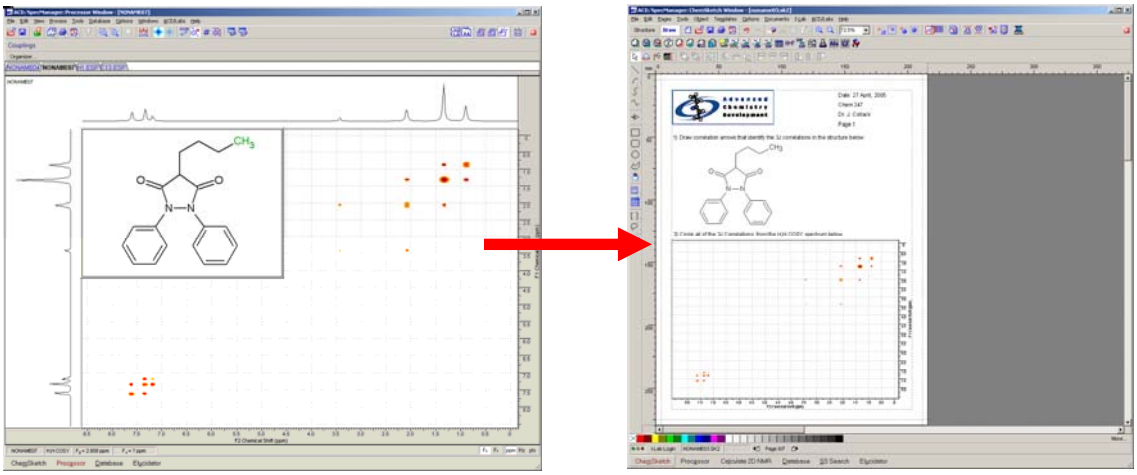

Figure 6. *After predicting a 2D spectrum, the user can create a new assignment or examination from a predefined template with one mouse click. Multiple types of 2D spectra can be combined in a single template and the structures can be left off of the examination, if desired.*

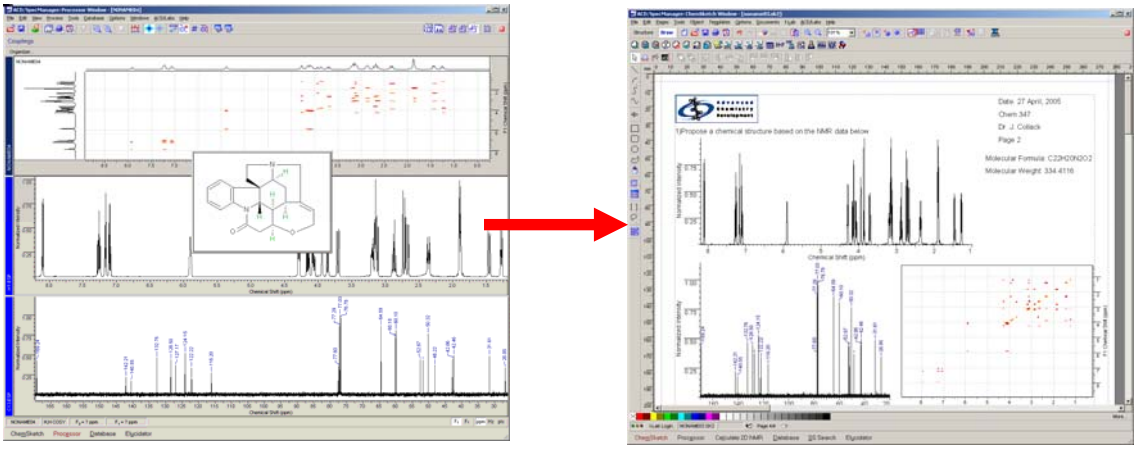

***Figure 7**. An example of a report containing both 1D and 2D NMR data..*

Understanding the Maze of 2D NMR Experiments

Perhaps one of the most difficult concepts to grasp initially in 2D NMR Spectroscopy is the wide range (and ever growing list) of different 2D NMR experiments that can be run. The difference between an HMBC and an HSQC may be a frequent topic of discussion in the classroom. ACD/2D NMR Predictor is capable of simulating any through-bond correlation experiment between ^{1}H, ^{13}C, and ^{15}N. This includes the following popular 2D NMR spectra:

- COSY
- TOCSY
- HSQC
- HSQC-DEPT
- HMBC
- HSQC-TOCSY
- INADEQUATE
- H, H J-Resolved
- C, H J-Resolved

This is a comprehensive list that will provide an instructor with a valuable resource to simulate and discuss all different types of 2D NMR spectra that a student may encounter in the future. This resource also provides the user with the flexibility to decide which compounds to study without having to spend the time running the actual experiment and allows the simulation of spectra for experiments that could not reasonably be run. Furthermore, multiple spectra can be open in one window, providing the option to compare two or more 2D NMR spectra (Figure 8).

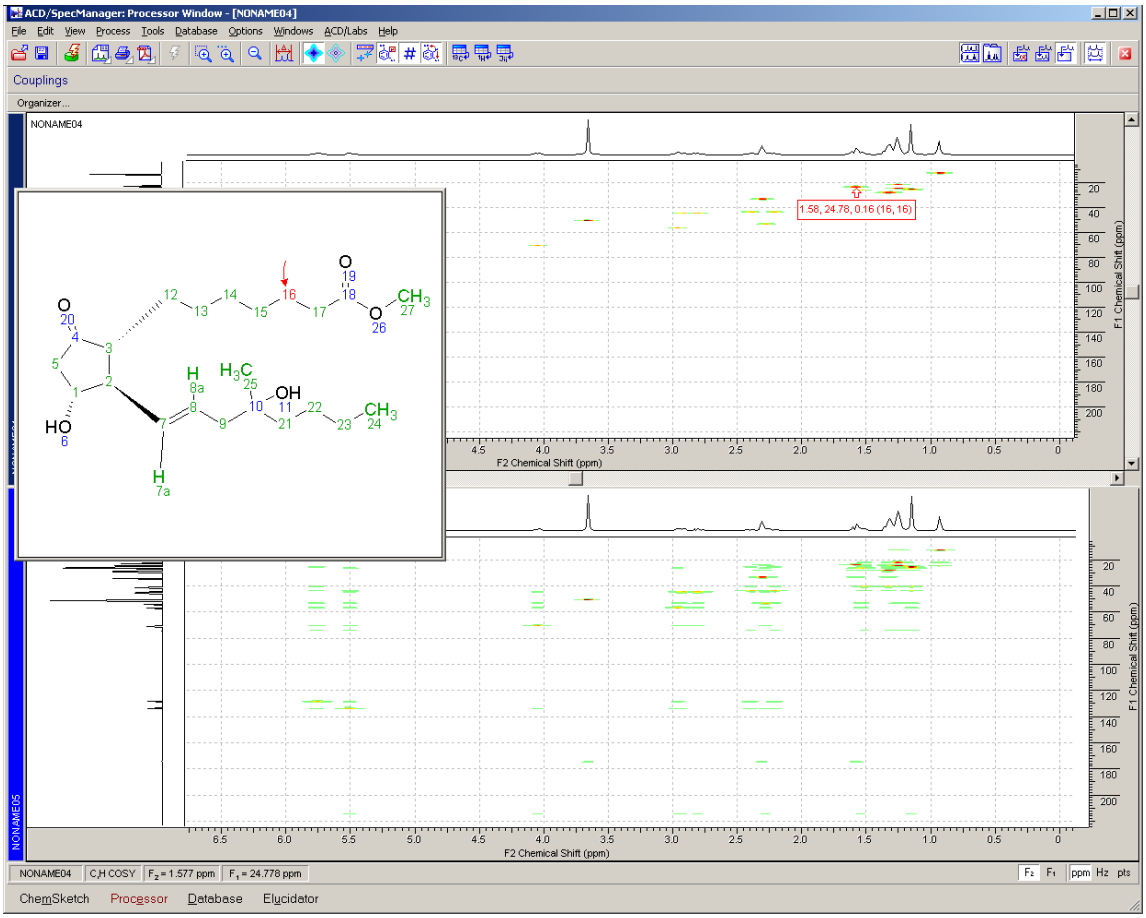

Figure 8. A comparison between predicted HSQC (top) and HMBC (bottom) spectra of Cytotec.

Having an understanding of the different types of 2D NMR experiments and understanding what experiments to run based on a certain compound is a very valuable asset for a student heading into industry. As well, some of the more sophisticated experiments can use hours to days of instrument time, which means running unnecessary experiments on the instrument is a waste of time and resources.

Conclusion

Teaching 2D NMR Spectroscopy can be a challenging endeavor, especially with limited resources. By not having the proper instrumentation or time to spend on running 2D NMR experiments, instructors are forced to use the “classical” examples of 2D NMR given in textbooks. This application note has highlighted how ACD/2D NMR Predictor can be used in the classroom as a visual aid to help illustrate different experiments and concepts encountered in 2D NMR Spectroscopy. In addition, examination and assignment templates can be created that allow the instructor to create different working examples with ease.

If you would like a free evaluation of this software, please contact Tricia Corrin at tricia.corrin@acdlabs.com.