Return to the **Winter'05 CONFCHEM**

Remote NMR Instrumentation in the Undergraduate Organic Laboratory

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In this paper I will present how we have used remote instrumentation in the sophomore organic chemistry laboratory at St. Olaf College to completely transform how NMR spectroscopy is carried out and how the concepts related to NMR spectroscopy are introduced. I will touch on the process we went through during the past few years to implement what we call 24/7 Dynamic NMR Spectroscopy, and I will show how the implementation we have put in place has enabled a completely new team-based approach to investigation by students at the sophomore level.

Three Problems

At the outset of this program, back in the fall of 2000, we felt the need to improve our access to NMR spectroscopy at St. Olaf College. Our old NMR spectrometer, a 1980s-vintage Varian Unity 300, had served us well, but we had continually been dogged by three intrinsic problems:

- Equipment: How does one make effective use of a very expensive ($400,000) piece of equipment at a small liberal arts college?
- Time: How can a substantial number (100+/year) of entry-level organic chemistry students be introduced to high-tech cutting-edge experimental techniques without overburdening the system?
- Pedagogy: How can students be encouraged to experiment on their own even at a relatively early point in their instruction?

Our feeling that even with 13 years of experience using NMR spectroscopy in the organic lab, we just were not making good use of our investment. The basic problem is outlined in Figure 1.

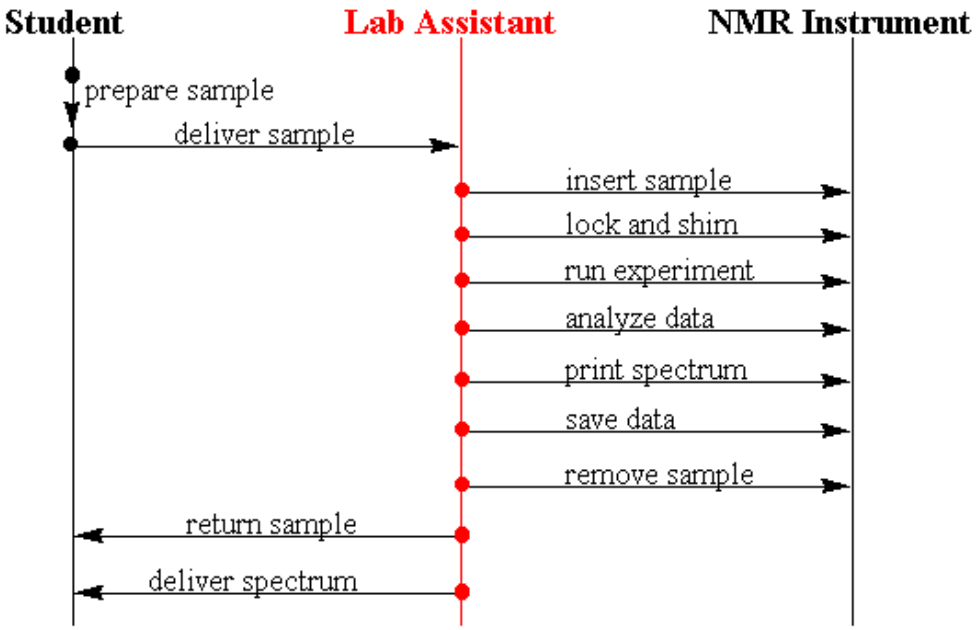

Figure 1. Prior to implementing automation, NMR spectra were run by lab assistants.

Our main problem was that with so many students and so little time (at least at the sophomore organic level), we just could not effectively introduce students to the immense power of NMR spectroscopy. The problem, of course, is intrinsic to NMR spectroscopy: In NMR spectroscopy, one needs to prepare and insert the sample, the instrument needs to be locked and shimmed, parameters need to be selected, data has to be gathered, and the data require sophisticated computer-based analysis prior to interpretation. Until just a very few years ago, "taking an NMR" had to be done manually, and this required substantial expertise.

Thus, the best we could do at the sophomore level was to show students the equipment and encourage them to watch as trained assistants carried out the experiments. We felt that this was inadequate, particularly because students at this point in their learning appeared to be particularly interested in experimentation. Here we had the most sophisticated experimental apparatus on campus, and we didn't have a way of getting students involved with it in any really valid way unless they were already actively involved in research.

The 24/7 Dynamic NMR Solution

With these ideas in mind, we set out in the fall of 2000 to find a solution to the three problems involving equipment, time, and pedagogy. Our goal was to transform the basic model of student/assistant interation with the spectrometer, as shown in Figure 2.

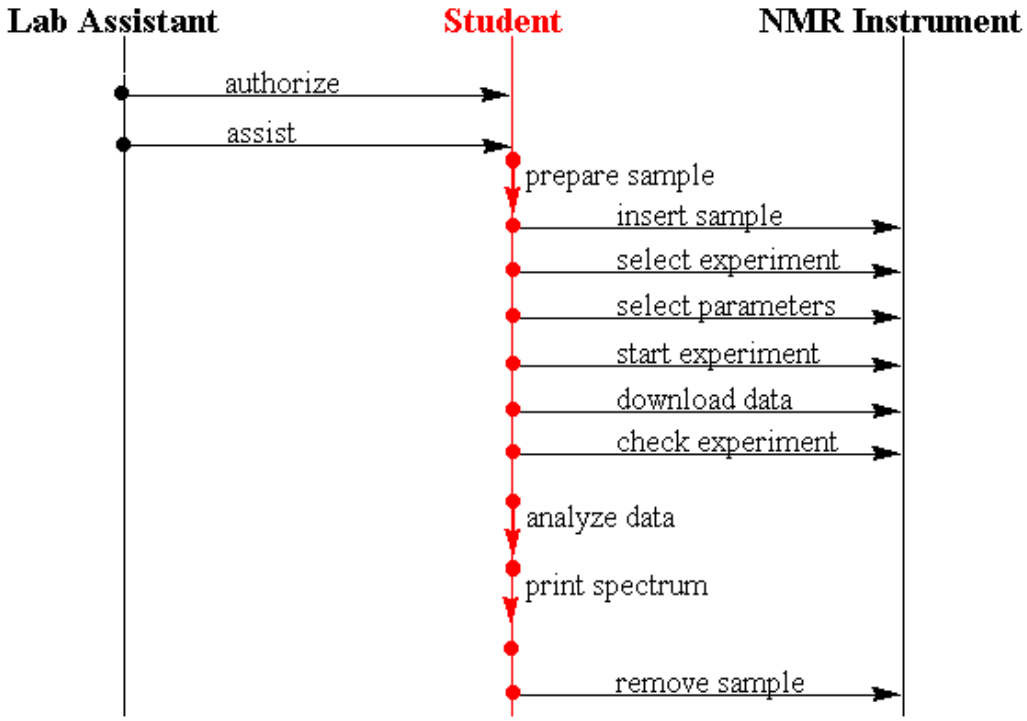

Figure 2. In our new paradigm, the lab assistant becomes the facilitator, and the student assumes responsibility for the NMR experiment.

Our goal was to design a system that allows the student to be in control of the experiment and the assistant to be just that, an *assistant*. In order to achieve this goal, we recognized that automation would be a key principle. We identified five necessary components of an automated system that would serve our undergraduate and faculty populations:

- Choose an NMR instrument that is designed with automation in mind, with the components needed for unattended operation.
- Design a simple yet effective web-based interface ("OleNMR") to distribute instrument access to any point on campus.
- Extend the "user" system already in place for E-mail and spectrometer use to a "team" system.
- Make the instrument available to students and faculty 24 hours a day, 7 days a week.
- Offer students the opportunity to try experiments that are not required but provide especially interesting and valuable information.

The first four of these elements are simply technological hurdles we had to overcome. I will not focus on how we achieved these technological goals in this paper, but will be happy to share them with any interested reader. The last point, involving student opportunity to experiment, is really the key to the pedagogical gains we have observed in implementing automation in the area of NMR spectroscopy at St. Olaf College. Because the system is automated, because it does not require direct operator intervention, because the NMR experiment no longer needs to be carried out strictly during "laboratory hours" or by "designated experts," because the control of the experiment can

now be in the hands of the student, students have access to a whole new *experimental* approach to NMR spectroscopy, as shown in Figure 3.

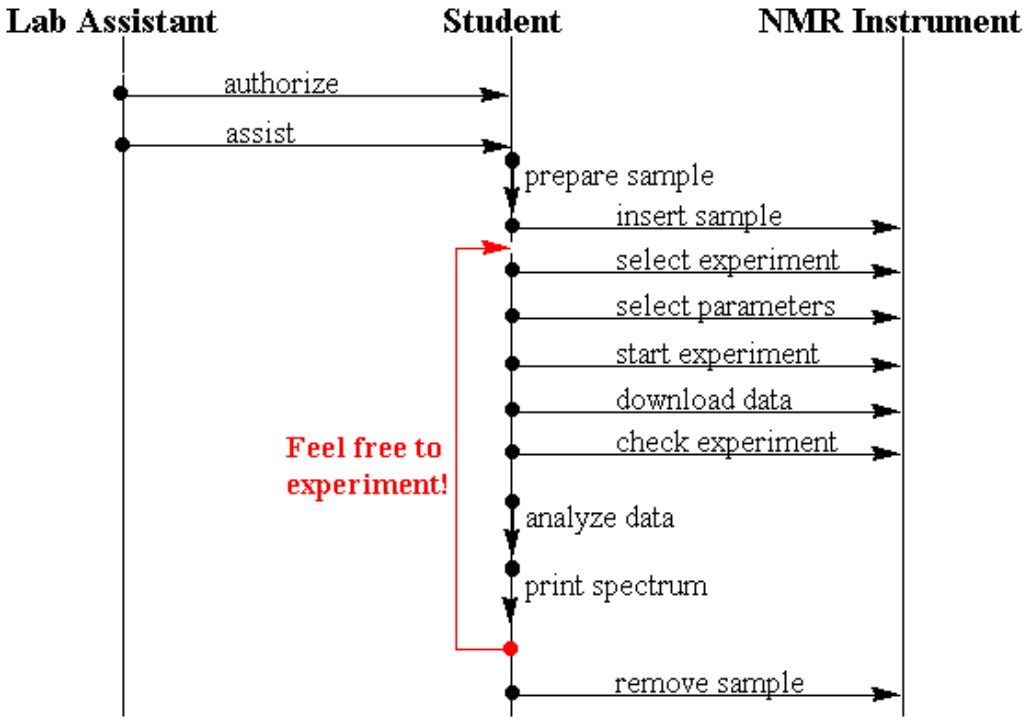

Figure 3. Automation allows for experimentation, because there is far less restriction in terms of instrument time.

In practice, 24/7 Dynamic NMR works as follows:

- Student teams in the organic laboratory are assigned sample changer positions at the beginning of the semester.
- At any time, students may insert a sample and run an experiment if the instrument is available.
- Once the sample is in the sample changer, the student may log on to the system from anywhere on campus anytime day or night using their favorite browser, set up an experiment, run it, analyze the data, and print the spectrum.
- Students are free to experiment on their own, within limits.
- Students in advanced courses have more direct contact with the instrument, and have a higher level of access to experiments.
- Authorized students doing research may have full instrument access.

Automation Enables Experimentation

The point here is that automation has enabled us to introduce a completely new way of using the technology of NMR spectroscopy in the undergraduate laboratory. More than that, what automation has allowed us to do is to transform the undergraduate laboratory itself into an opportunity for students to *experiment* in the authentic meaning of the word.

There are two fundamental ways in which automation has allowed students in organic lab to experiment. First, because the sample is in a robotic sample changer, students are encouraged to try more than just one "standard" NMR experiment. Thus, when I am supervising an organic lab, I ask that students show me their spectra. Even with absolutely no background in NMR spectroscopy, students know that there is information here, and we talk about what it means. "This is a very cool proton spectrum. Can you please take a carbon-13 spectrum and get back to me?" "Hmm, that didn't seem to give us much information. How much sample did you use? Could you add some more and try again?" "Oh, here's a beautiful spectrum. Good job! Say, would you be willing to try a COSY experiment? It only takes about 10 minutes. We can talk about what a COSY experiment is when it's done."

In addition, automation has allowed us to use the spectrometer essentially exactly the way it is commonly used in research laboratories. That is, as a powerful diagnostic tool for the success of a synthetic reaction. "CONGRATULATIONS! This spectrum tells me that your experiment worked. Look here...." "Ah, I see you could have rotovapped that a little longer. This signal here is for ethyl ether."

Automation Allows Earlier Introduction to NMR Spectroscopy

What's most interesting to me is that this use of NMR does not require *any* prior knowledge by the student about the theoretical basis of the NMR experiment. In fact, what we have observed at St. Olaf is that by providing students with NMR data of their own early on in the course, long before NMR is introduced in class, many become highly motivated to learn more about it. Long before they know all about chemical shift, integration, and splitting, they have learned that the NMR technique answers the most practical of questions: What happened? Did I get the right product? Is it pure? Why is the melting point so low?

For example, because it is so easy to implement, we now introduce NMR spectroscopy during the very first week of lab in organic chemistry. In this experiment, students are given an "unknown" solid and have to determine its identity. A list of approximately 20 possible compounds, with their known melting points, was posted in the laboratory. While in some sections of the course, students attempted this solely based on melting point and solubility properties, in other sections students also took proton and, in some cases, C-13 NMR spectra. With spectra in hand, students were given just a little in-lab introduction to the ideas of NMR spectroscopy, such as where aromatic protons appear and what an OCH3 would look like. Students easily learned with just a very brief introduction how to determine the number of nonequivalent sets of protons or carbons based on structure. Using their spectra, students could then easily rule out compounds that had similar melting points. In several cases students learned that taking good melting points requires more effort than they expected, since the listed compound with the nearest melting point was ruled out by the NMR data. The extra work of looking up compounds in the Aldrich catalog to determine their

structure was rewarded with definitive correlation between structure and NMR spectrum.

Automation Encourages Teamwork

Team (American Heritage Dictionary of the English Language):

1. A group on the same side.
2. A group organized to work together.

In the organic laboratory at St. Olaf College students regularly work in teams of two or three. In addition, it is useful to consider the lab assistant and supervising professor as additional team resources. Thus, we wanted our automated NMR spectrometer system to work in a team context and to reflect that approach. The teams involved with NMR spectroscopy at St. Olaf College are organized based on two broad categories: course and research. Each of these "teams" is subdivided into a series of more precisely defined teams, providing a whole series of working groups (Figure 4).

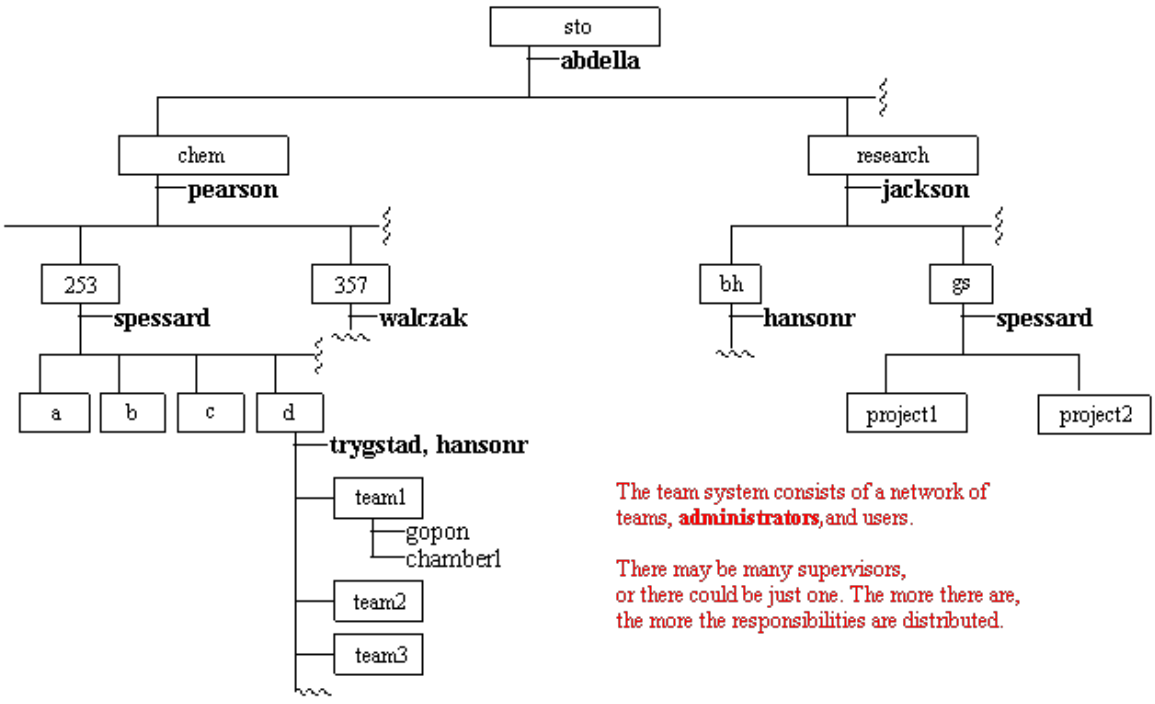

Figure 4. Teams are set up either in terms of courses and sections or research groups and projects.

In this way, the concept of a team need not be restricted to laboratory courses. A professor doing research that involves NMR spectroscopy could set up any number of teams related to their work.

We implemented three classifications of team members:

- Experimentalist (students) Experimentalists design and submit experiments, monitor instrument status, and analyze data. Generally experimentalists work in teams of two or three students. The idea is that each member of a team has equal access to the instrument. All team members see the same files, join in the responsibility for designing and submitting experiments, and are free to analyze the data either collectively or independently.
- Assistant (laboratory or research assistants) Assistants add and delete team members, assign and identify samples, and help experimentalists with instrument operation. Each lab section, for example, involves a lab assistant. The primary responsibilities of the lab assistants include (a) assigning students to teams and (b) helping students interact with the instrument and interpret the data. (Note that it is expressly not the lab assistant's job to carry out the NMR experiment. That job falls squarely on the student experimentalists.)
- Supervisor (professors) Supervisors create teams, set experiment availability and options, allocate sample changer slots, help students and assistants interact with the instrument, and oversee the server file system. While in principle there might be just one supervisor (the "system manager"), the idea here is to distribute this responsibility to more than one individual. Thus, any supervisor may create new teams under their particular jurisdiction.

The Importance of Context

One of the interesting benefits of our team model is that context is everything. It is most important to understand that a real person might play more than one of these roles. When a team member logs in, they also select a team in order to provide a context for their work (Figure 5).

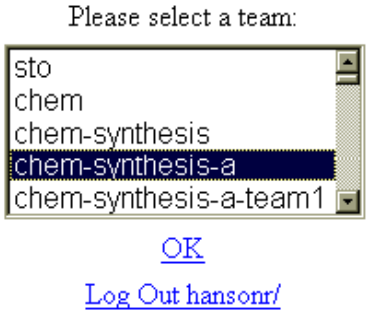

Figure 5. Selecting a team context.

For example, a supervisor might play the role of an assistant (assigning samples) or an experimentalist (running experiments). The user "skladzie" (a junior chemistry major) may be an assistant for chem-synthesis-d, for example, and also a general user in chem-physical-team2.

Access to spectrometer function is based on the team that is designated at log in. A person logging

in as a member of "chem-synthesis-d-team1" sees only the data that their team has produced (or is given access to) and has access only to the sample changer slots assigned to their team. Likewise, a supervisor or assistant logging in as that team sees what the student sees, though they would have certain additional rights. As a supervisor or assistant, I can log in as any of the teams under my supervision. When I do, I see what that level of user would see. I can log in as "chem-synthesis-d" and see all the spectra recently acquired by section D; I can log in as "chem-synthesis-d-team3" and see just what that team has done. And, of course, I can do this from my office, not just at the spectrometer. Similarly, an assistant can log in either at his or her default level or as one of the teams under their supervision.

Typical user systems (such as E-mail), even though they may involve working groups (aliases), don't really support group work. The 24/7 team concept fosters group work, because all users, once logged in, work exclusively in the context of a team. Although I may be a member of more than one team, by logging in as a specific member of a specific team, the system automatically helps me focus my activities. As a supervisor, this is particularly useful, because I can log in as one of the teams under my supervision and focus specifically on what the members of that team are working on. By allowing all team members equal access to the original data (not just copies), the system supports true team work. Alice might start an experiment, but Bill might be the one to analyze the data and suggest improvements. The division of labor is up to the individual teams.

One of the goals of the team system is to distribute management functions so that no single person is overburdened. There may be a principal supervisor who sets up the teams and adjusts them periodically, but other supervisors can certainly set up teams of their own. Management of team member lists is the responsibility of the assistant-level management team. These players use very simple tools to add and remove users from teams. The username base is drawn from a campus-wide database and needs no particular management.

Automation Requires "Fair" Queuing

One aspect of the system that took considerable thought was the implementation of a method by which requested experiments could be ordered in a way that a majority of users would consider "fair." This was necessary because an automated system, at least in this context, is a multi-user environment. Unlike our old spectrometer, with one seat, our new spectrometer has hundreds. "First-come, first-served" just didn't seem like the right approach.

In addition, the "factory default" queuing routine built into Bruker's IconNMR system was designed for a completely different use of the sample changer. Designed with high throughput in mind, this routine would cycle through all samples sequentially, running all designated experiments for each sample in turn. The basic philosophy was that one would load up the sample changer, designate the experiments to run using IconNMR, set it going, and walk away. While this certainly makes for efficient use of the sample changer, it was not sufficient for our needs because it was sample-oriented rather than team-oriented.

For these reasons we implemented the following rules:

1. Number of experiments: You may submit as many experiments as you like. If another experiment is running, your experiment will enter a queue with the status pending. When it is

your turn, your experiment will automatically run.

2. Order of Execution: The queue is not a simple first-in-first-out queue, because if it were, one team could submit a large number of experiments and tie up the queue. Rather, if other teams have experiments queued and you have more than one experiment in the queue, only your first experiment will advance. Once it has run, then your next experiment will advance. Thus, if one team submits five experiments and another team submits five experiments after that, the experiments will run in an order that alternates between teams. Similarly, if three teams submit experiments, then there will be a three-way rotation as experiments are run.
3. Composite experiments: Some experiments may involve more than one spectrum. These composite experiments are run as a set.
4. Canceling experiments: You may cancel any of your experiments at any time, even after it starts running. If an experiment is canceled before it starts running, it will be removed from the queue and its status will change to canceled. If an experiment is canceled after it has started running, its status will change to aborted, and data may be lost.
5. Temporarily suspending experiments: You may suspend (put on hold) any experiment that isn't already suspended or running. Suspended experiments will remain in the queue indefinitely and may be reinstated or canceled. If reinstated, an experiment will be returned to the end of the queue.
6. Changing the order of jobs: Supervisors may at their discretion expedite a job, putting it to the top of the queue, or suspend/reinstate a job, which will place it at the end of the queue.

The implementation of these rules primarily amounted to rewriting a single TCL function in a single module of Bruker's IconNMR code. In addition, we developed a JavaScript-based monitoring system that allows users to check the current instrument and queue status (Figure 6).

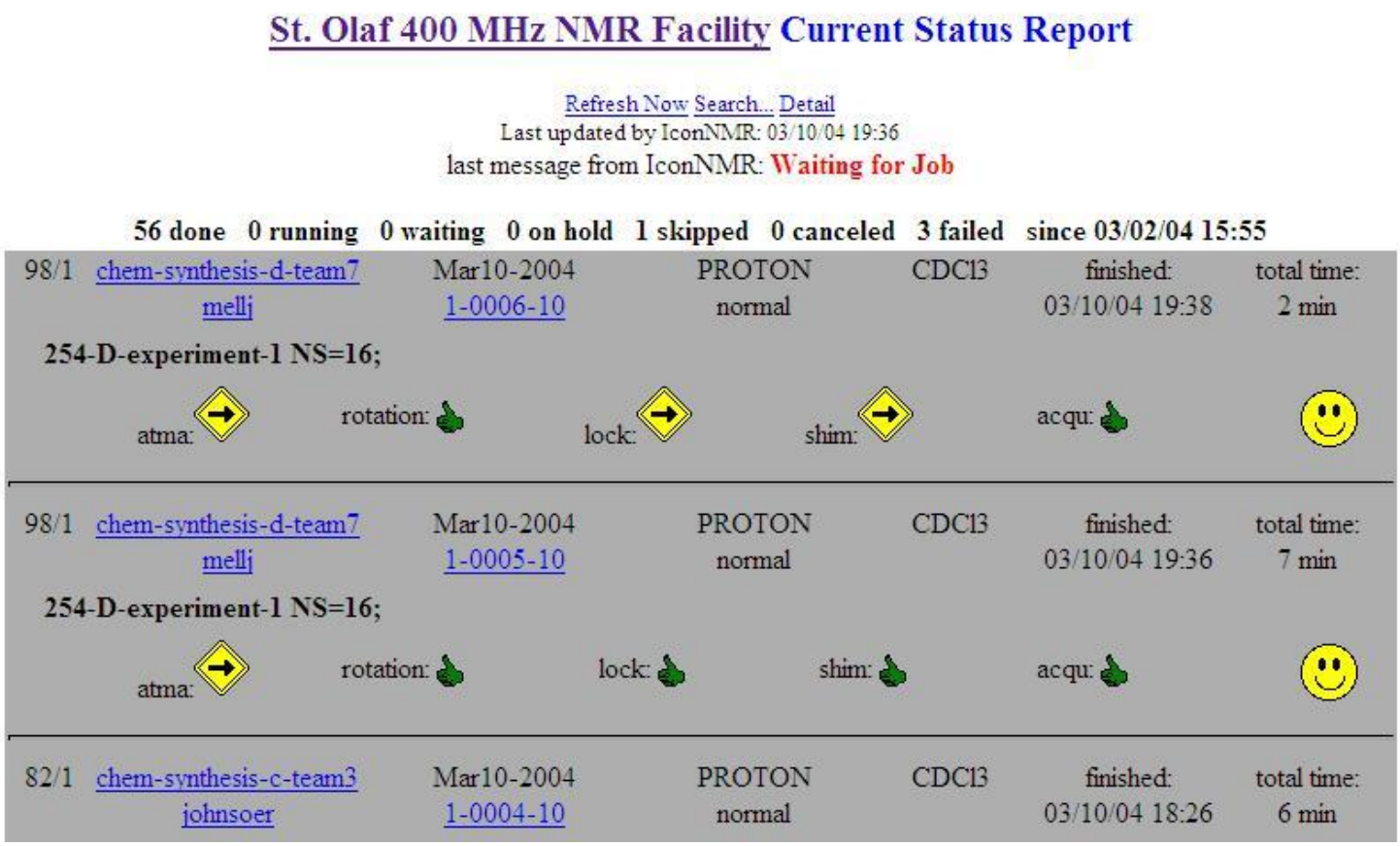

Figure 6. The status page.

Advantages of Automation

I hope it is clear from the above description that automated NMR has completely changed our use of this technology in the organic laboratory. Students have had far more access to NMR than ever before and can experiment with techniques not specifically called for in the laboratory manual. NMR can be used in lab in the way it is used in research: as a diagnostic tool for answering practical questions related to how an experiment is going or how successful it was. In addition, because we are now able to introduce NMR spectroscopy so early in the sequence, when it comes time to discuss NMR in class, students already have a context and even a fair amount of experience with real problem solving using NMR.

For the lab assistant, automated NMR completely transforms their role. No longer are they sitting in a room running spectra or explaining over and over to students how to lock, shim, acquire, and analyze spectra. Instead, they assist in the assignment of teams and sample positions, and they get students started with sample preparation.

For faculty, who often were heavily involved with training of assistants and students on the detailed technicalities of getting "good" spectra, automated NMR has released them to do what they far prefer to do: assist in the selection of appropriate NMR experiments and in the interpretation of spectral data.

Clearly, for the spectrometer, being able to have it in active use any time day or night is far better

than trying to fit all student use into blocks of time determined by the registrar. One of the most interesting results of automation has been the effect of "down time." With the traditional approach to NMR spectroscopy, when the machine went down, it was a disaster. Samples backed up; whole sections went without data. We have had our share of times when the machine was not available. For example, when the hard disk crashed it took a full day to put in a new drive and reinstall all the software. While this was happening, amazingly, nobody cared. Students loaded the sample changer as usual during lab and, upon getting an email from me that the system was back up, started submitting experiments from wherever they were on campus at that time.

In summary, advantages of 24/7 Dynamic NMR are several:

- For Students:
  - opportunity to experiment
  - better integration of class/lab experiences
- For Lab Assistants:
  - more effective use of assistants as lab assistants
  - more interaction with students in and out of lab
- For Faculty:
  - more time for teaching during lab rather than playing the technician role
  - focused "as needed" instruction in spectroscopy
- For Instrumentation:
  - more efficient use of the spectrometer
  - fewer problems with down time

Implementation Details of 24/7 Dynamic NMR

This paper is not intended to explain all of the implementation details of our system. Basically, though, we have a Bruker Avance 400 MHz spectrometer with automatic tuning/matching Z-gradient broadband probe with deuterium gradient shims (Figure 7), and a BACS-120 sample changer (Figure 8), all standard issue from Bruker.

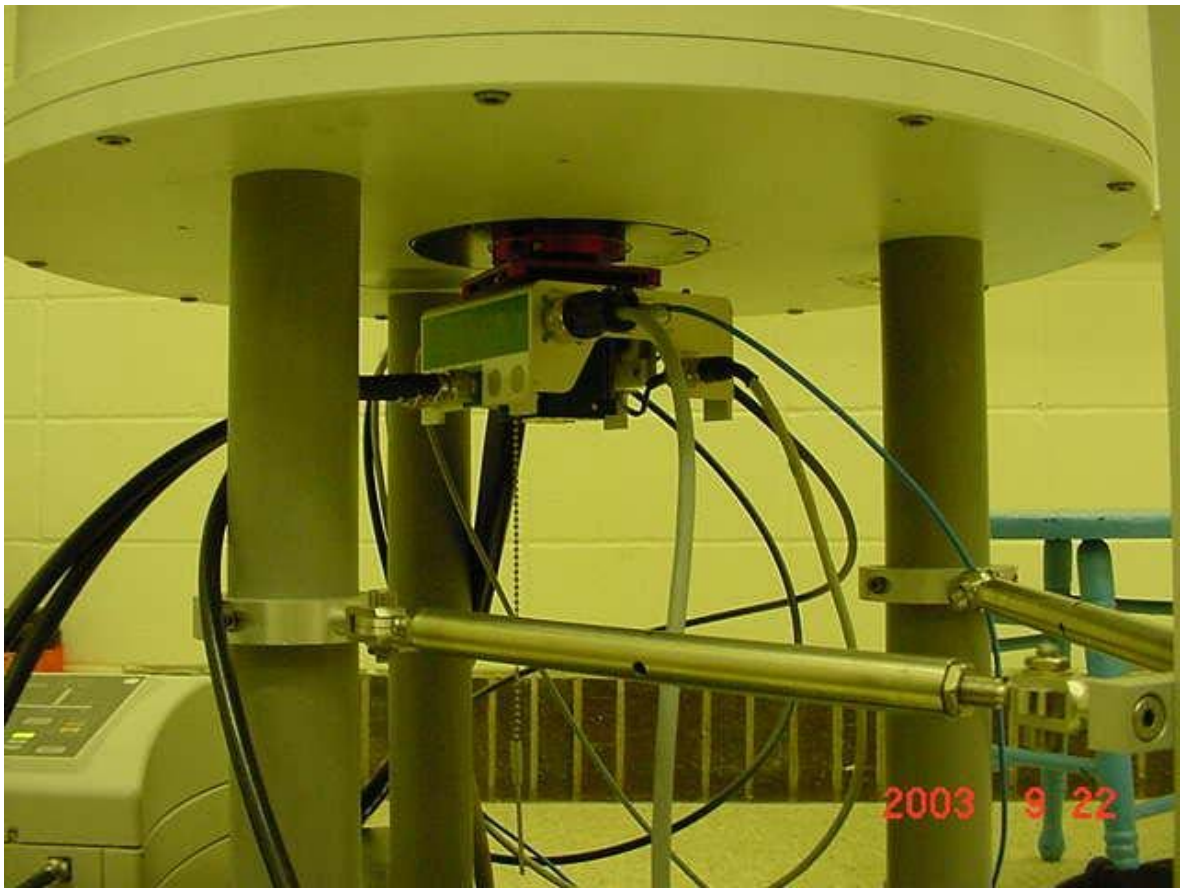

Figure 7. Bruker automatic tuning/matching Z-gradient probe.

Figure 8. Bruker 120-position automatic sample changer (BACS-120) with two concentric rings of sample positions.

We are basically tapping into the Bruker "IconNMR" system. On the Windows-based PC that runs the spectrometer, we made some minor modifications to the Bruker open-code TCL language routines and introduced a small suite of Visual Basic-based communications software (DDESERVE, OLENMR).

In addition, on a separate campus server, a set of client JavaScript files gets loaded onto the user's machine as the website is accessed. Development of this code was by far the most complicated aspect of the project and involved two full summers of work and five research students.

One of the greatest challenges was the design and implementation of a system by which spectral data could be manipulated remotely -- integrated, enlarged, expanded, and printed. After considerable work we settled on a method that allows real-time manipulation of a moderately precise spectrum (Figure 9) followed by delivery of a full-precision spectrum in the form of a PDF document (Figure 10).

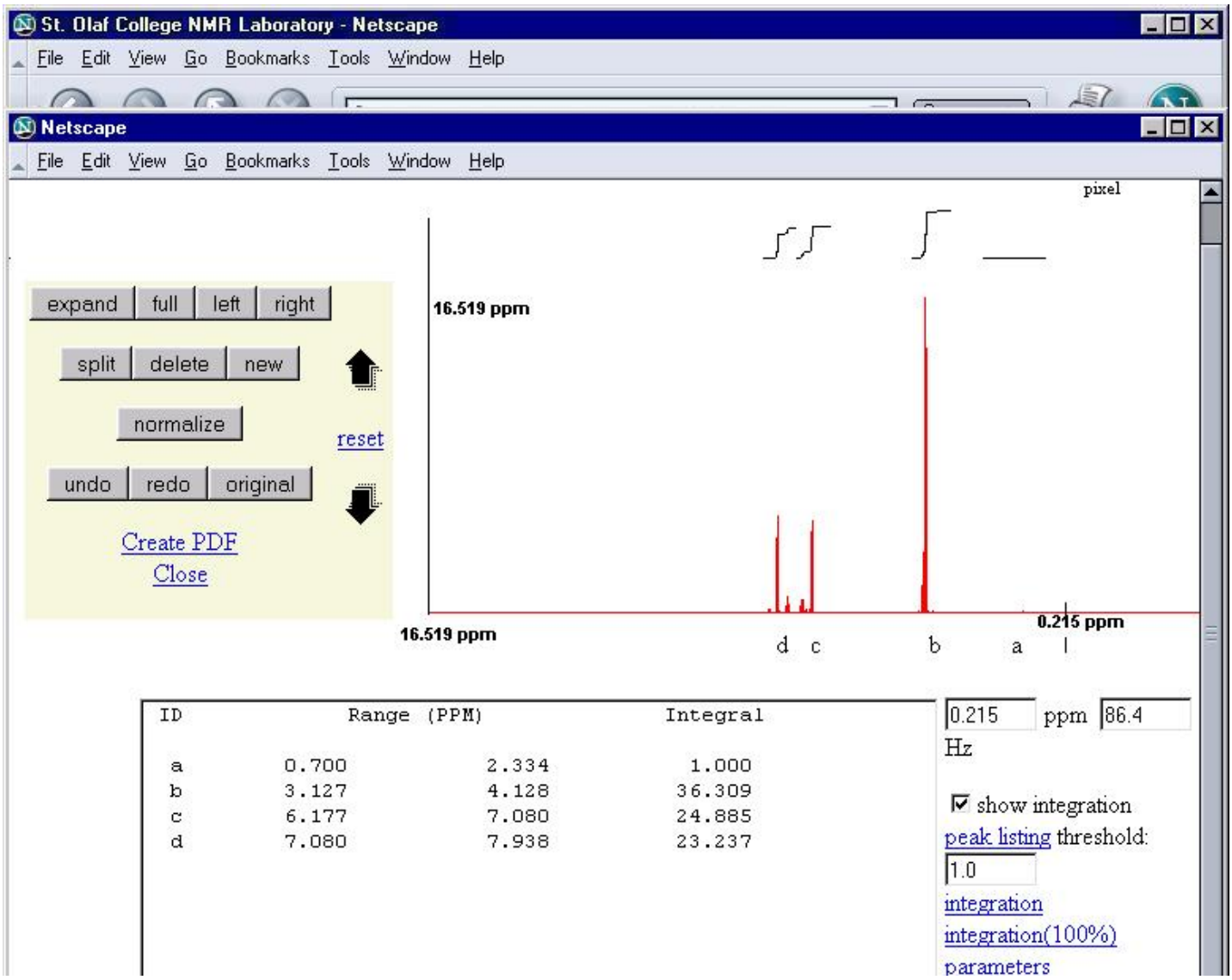

Figure 9. The interface allows for quick integration and expansion.

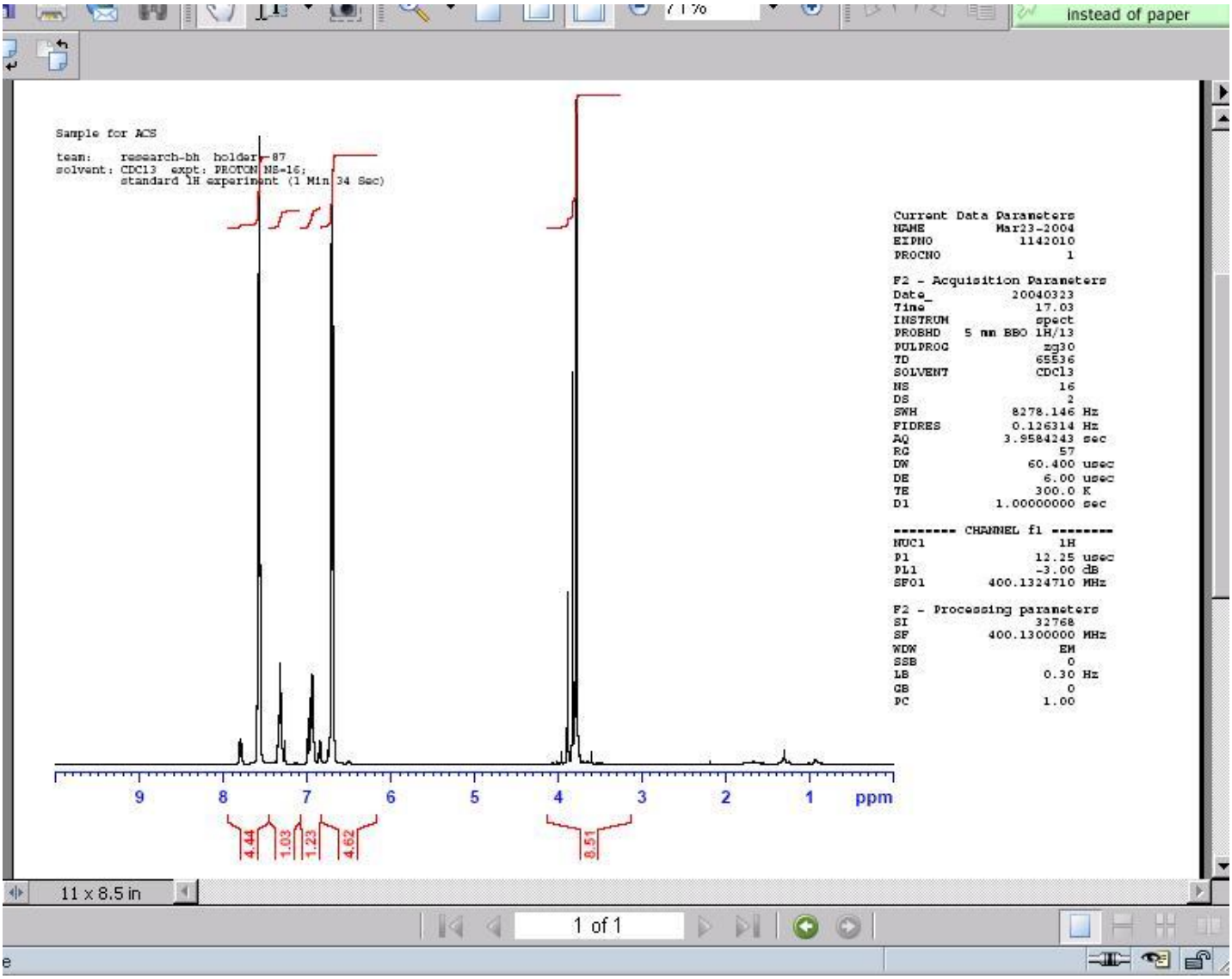

Figure 10. Final delivery is in the form of a PDF file.

Remote spectral phasing has not been implemented, but it also has not been necessary. (For research groups with higher demands, the system offers delivery of the FID in JCAMP-DX format for full remote processing.)

In all, the operation is totally transparent to the user and is relatively easy to implement and manage. The final gratification, of course, is in seeing satisfied customers (Figure 11).

Figure 11. Chemistry students using the 24/7 Dynamic NMR system.

Acknowledgments

This project could not have been possible without the overwhelming support of the administration of St. Olaf College, which, after two unsuccessful attempts at NSF CCLI funding ("too ambitious"/"not hands-on"), kicked in $500,000 for the acquisition of a new NMR instrument and the necessary building renovations. Clemens Anklin, Bruker Biospin, was the first to say that our crazy idea was conceivable on a Bruker system. His confidence in our plan is greatly appreciated. (Engineers at another vendor resoundly put down the idea as totally unfeasable.) Chemistry majors Mike Purnell, Gregg Sydow, and Stephanie Skladzien (summer 2002) and physics majors Jared Irwin and Bryan Anderson (summer 2003) contributed tremendously to the design and implementation of the client-side JavaScript coding that has made the interface almost trivial for use by novice undergraduates. Finally, I thank my colleagues in the Chemistry Department at St. Olaf College for their patience and enthusiasm during the development of this novel way of utilizing NMR spectroscopy.

P.S.

If you are interested in automation in the undergraduate laboratory and planning to be at the 229th ACS National Meeting in San Diego, California, in March 2005, please join us for the symposium Automation and Remote Access Technology in the Undergraduate Teaching Laboratory Wednesday afternoon, March 16.

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