

History of the Harvard ChemDraw Project

David A. Evans*

Chemdraw · computer graphics ·
molecular structures · structure representation

Dedicated to Professor Norman C. Craig

Chemical Hieroglyphics

Organic chemists routinely communicate concepts through a combination of cursive statements and graphics-based molecular representations commonly referred to as valence bond structures.^[1] This form of written communication may be loosely compared to the structure of the Egyptian hieroglyphic language which combines both cursive and icon-based graphics (glyphs) to communicate a specific thought or statement. The importance of “chemical glyphs” may be highlighted by the fact that two chemists not sharing a common language may effectively communicate through the use of a series of valence bond structures and associated “curved arrow” notations.^[2]

Life before ChemDraw^[3]

Until the introduction of computer-based structure drawing programs in the mid-1980s, publication-quality chemical graphics were generally produced by an on-campus or departmental graphic arts facility. Leroy Lettering Sets^[4] were invariably used to produce india ink drawings on vellum, a parchment-quality paper (Figure 1). These sets provided a collection of templates of various font sizes. Bold and italicized letters each required the requisite template and pen. The specialized pen facilitated the transcription from template to vellum. Helvetica was the only font option. The various ring sizes were usually drawn with the aid of a template such as the Fieser Triangle (Figure 1).^[5] It was the rare student who ventured into this realm of technical complexity due to the time commitment. Generally, students used the Fieser Triangle, a pen, and dry-transfer letter decals to generate structures. Dry-transfer decals of both regular and curved arrows were also readily available. By any measure, drawing chemical graphics was a labor-intensive task that one had to face in the preparation of both publications and theses. Students who spent too much time on this activity did so at the risk of making insufficient progress in the laboratory.

Xerox Star Workstation^[6]

In 1981 the Caltech Chemistry Department began to evaluate a sophisticated workstation under development by Xerox.^[7] This workstation cluster was significantly ahead of its time. Technically, the term “Star” referred to the software user interface that was the creative nucleus of the product. This interface included the introduction of the hierarchical file/folder system, the mouse, and a full-screen (WYSIWYG) monitor for distortion-free drawing.^[8] These were the critical attributes that were ultimately incorporated into many of the modern personal computers, including the Macintosh several years later.

Ultimately, Caltech elected not to adopt the Star workstation cluster, and Xerox did not commercialize this product line. In the interim, I did purchase one workstation (\$32 000) to become familiar with the Star user interface. Unfortunately, no chemical structure drawing programs were available at that time.

Institutional Moves Are Good for Science

It has been my long-held view that professors should avoid becoming too comfortable in their environment. It is quite easy to fall into an established pattern of thinking. The impact of changing universities forces one to re-evaluate the quality and direction of one's science. These circumstances motivate one to refresh one's research program through a change in environment, people, and introspective analysis. Such was the case with my move from Caltech to Harvard during the summer of 1983. Upon our arrival in Cambridge, the Harvard Chemistry Department set up temporary labs in the basement of the Converse and Conant laboratories. These were the labs recently vacated by the Corey group for renovated space in the Conant Laboratory. Once on site, we began the design of our permanent labs on the third floor of Converse. Historically, this space had been occupied by Professor P. Bartlett (1934–1974), and subsequently by Professor P. Wender (1974–1982). Our group moved into these renovated facilities in February 1985 as its third-generation occupants.

Selena (Sally) Evans^[9]

During the Caltech–Harvard transition, my wife Sally, who had been a high school teacher for more than 20 years,

[*] Prof. D. A. Evans
Department of Chemistry & Chemical Biology
Harvard University, Cambridge, MA 02138 (USA)
E-mail: evans@chemistry.harvard.edu

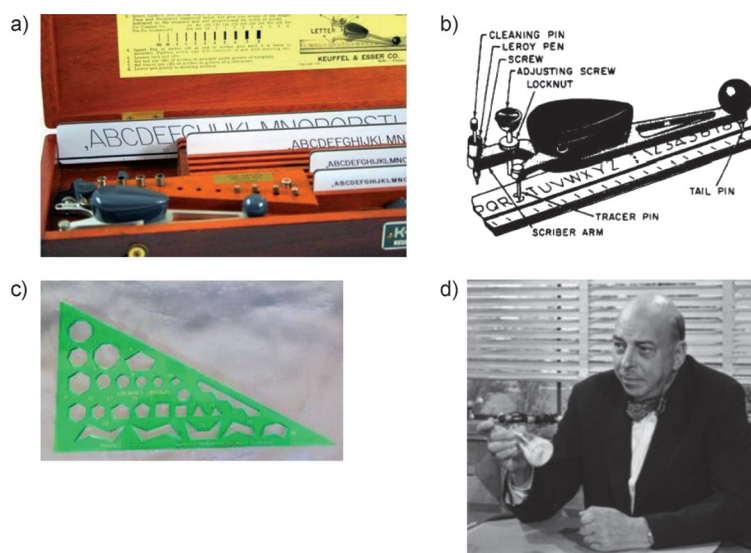


Figure 1. Miscellaneous drawing tools for producing chemical structures: a) Leroy Lettering Set (Keuffel and Esser Co.), b) Leroy Lettering Pen, c) Chemist's Triangle developed by Professor Louis Fieser (1899–1977; portrait in (d)) at Harvard University.

elected to work with me to get our lab set up and on its way. She served as my group's administrator, laboratory architect, and graphics artist during the relocation. She was particularly effective as a lab designer and had acquired drafting skills in high school. After the dust settled, and all of the laboratory setup funds had been expended, she returned to her interests in teaching. For the record, Sally was well trained at Oberlin College in the physical sciences. While at Oberlin, she designed her own undergraduate course of study that was directed toward the teaching of physical science and math courses at the middle and high school levels. While pursuing her chemistry major, she augmented her knowledge in other science courses such as astronomy, geology, and physics. During her career, she regularly taught chemistry, physics, mathematics, astronomy, and earth science for more than three decades in private schools in California and Massachusetts.

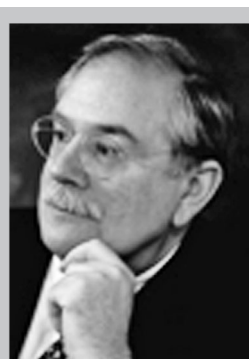
The Macintosh

In January 1984, Apple introduced the Macintosh, in a now-famous TV advertisement during Super Bowl XVIII, to much fanfare. At the end of the advertisement, the following statement appeared: "On January 24th, Apple Computer will introduce Macintosh, and you'll see why 1984 won't be like '1984'."^[10] Kevin Maney, a decade later in *USA Weekend*, published an article entitled "Apple's '1984' Super Bowl commercial still stands as (a) watershed event." He also observed that, "Twenty Super Bowls later, many tech industry leaders say the ad and the first Mac played an inspiring role in their career paths. It was one of those rare bolts of lightning that can mobilize a generation in a particular field—the way John F. Kennedy's call for a man on the moon motivated the aerospace crowd, or Bob Woodward and Carl Bernstein rallied young journalists with their Watergate investigation."^[11]

By early 1985 Sally and I decided that we needed our own Macintosh; accordingly, we joined the revolution and purchased a second-generation Mac (512 K) for the modest cost of \$3200, one-tenth the cost of the Xerox workstation. Surprisingly, the Mac came equipped with a user interface remarkably similar to the Xerox Star system. In this context, Steve Jobs provided Apple stock to Xerox for access to the Star user interface. As an aside, I had been passively hoping for the development of a chemical drawing program even during my time at Caltech. Once we saw the capabilities of the MacDraw program,^[12] it was clear to us that there was the realistic opportunity of developing a program for the creation of chemical structures at a reasonable cost. Accordingly, the Mac was the obvious choice.

Stewart Rubenstein^[13]

In 1985 Stewart was an NSF-sponsored graduate student pursuing his PhD degree as a student with Professor E. J.



David Evans received his AB degree from Oberlin College in 1963. In 1967 he obtained his PhD in Organic Chemistry (with R. E. Ireland) at the California Institute of Technology. He joined the chemistry faculty at the University of California, Los Angeles as an assistant professor. In 1974 he returned to Caltech, in 1983 he joined the chemistry faculty at Harvard University, and in 1990 he was appointed as the Abbott and James Lawrence Professor of Chemistry at Harvard. Evans has made significant advances in the design of stereoselective reactions and the applications of these processes to natural products synthesis and asymmetric synthesis design.

Corey. Stewart was integrated into that group as a member of the LHASA^[14] effort. In September 1984 Stewart had also purchased a Mac, and he frequently visited our labs down the hall. He soon became interested in Sally's activities in slide preparation. She was producing india ink drawings with a Leroy Lettering Set (Figure 1). One of her frustrations was associated with the effort expended in creating a complex structure only to start over to draw the next structure in the reaction sequence where only minor chemical modifications had been made. On more than one occasion she suggested that I might consider working on structures less complex than vancomycin!

One afternoon during this period, Sally vented her frustration with the comment to Stewart: "How would you like to save my marriage?" In fact, this was a loaded question as she and I had already looked at the MacDraw software that appeared to be a reasonable starting point for a Mac-based structure-drawing program. This interaction culminated in a meeting between Sally, Stewart, and myself to discuss the possibility of creating such a program. Stewart stated that he would have a go at this challenge. Within several weeks he reported back with a rudimentary program that could handle many of the templates found on the Fieser Triangle. In his first rendition, the length of the line or the size of the ring was determined by the magnitude of the "drag" of the mouse from the "touchdown point." Sally then informed him that, while this feature was terrific, she also wanted to have the option of making all of the bonds the same length! Stew's response: "Why would you want to do that?" So began our meaningful collaboration into what was needed for a chemical drawing program for the chemical community. Arguably, the best piece of advice that I gave to Stew was that the esthetics of the drawn structure had to be as good as, or better, than that rendered by a professional graphics artist. With several notable exceptions, chemists are quite particular with regards to the quality of the structural graphics in their manuscripts and slide presentations. Here are a few of the issues that were addressed in creating the various drawing tools.

Reaction Arrows

When Stewart asked what arrowhead sizes were needed, Sally provided him with a sheet of dry-transfer arrowhead decals that she had been using. They provided the frequency with which each arrowhead size was used along with the dimensions of the arrow (Figure 2). We then went on to introduce curved arrows and arcs, and finally custom arrows that used the Bezier drawing tool (see below).

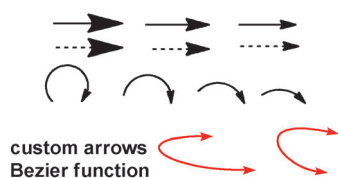


Figure 2. Selection of arrow types.

Wavy Lines

Since structures **A** and **B** illustrate the same issue—the lack of stereochemical information at the R-substituted stereocenter—I felt that the wavy line function was not really needed (Figure 3); accordingly, I lobbied to not incorporate this tool. Nevertheless, by popular demand from the external users, this tool had crept into program by 1990. As I anticipated, the wavy line function has been widely abused. In my opinion, the graphic that represents the ultimate insult is a structure with two such wavy lines emanating from the same carbon!^[15]

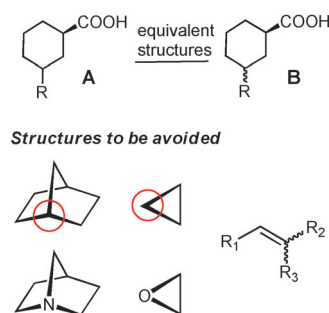


Figure 3. Wavy and intersecting lines.

Intersecting Lines

Stewart expended much effort in dealing with line intersections (Figure 3). In many of the early beta versions of ChemDraw, the intersecting lines did not blend together smoothly, and the appropriate location of atom symbols only magnified this complex problem. In retrospect, this is an understandable problem as one has two converging bonds, at all angles, and an atom symbol converging to a single point.

Atom Symbols

As Stewart noted to me, "One other notable challenge in producing high-quality drawings was producing consistent positioning and spacing of atomic labels; this required an inordinate amount of work, and was doubly difficult to achieve on the Apple LaserWriter."^[16] These are the kinds of challenges that one generally brushes over in the preliminary analysis of the problem.

Bezier Drawing Tool

This feature was introduced in the late 1980s as a result of personal lobbying efforts. There was a real need to draw transition state potential curves (Figure 4). This tool may also be used for producing custom arrows by adding arrowheads to one or both of the ends of the curve (Figure 2).

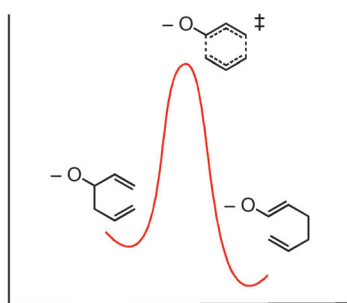


Figure 4. Bezier drawing tool for transition state diagrams.

Introduction of ChemDraw

In July 1985, I had been invited to present a lecture at the Gordon Conference on Reactions and Processes. We selected this occasion to advertise the ongoing development of the ChemDraw program. As there were no lectures scheduled for Wednesday afternoon, Stewart, Sally, and I set up a demonstration in the conference center at the New Hampton School (NH, USA). This occasion was reinforced by the fact that we had the conference participants' undivided attention since a midweek rainstorm kept everyone from dispersing to the woods, volleyball, and tennis courts. We brought our two Macs into the conference center and provided tutorials and hands-on demonstrations of the program. It proved to be a terrific success! I recall many aspects of that afternoon. In one instance, Scott Denmark (Illinois) worked diligently to draw a representation of a dodecahedron. The only downside to the occasion was that the Apple LaserWriter had not yet been made available to the market!^[17] While we brought along a dot-matrix printer to fill the void, it proved to be a meager demonstration of what was to come. Nevertheless, the fire had been lit, and the organic community quickly fanned the flames.

In August 1985, during one of my regular consulting visits to Eli Lilly (Indianapolis), I gave an informal demonstration of ChemDraw (CDβ-0.48) to the Lilly chemists. One of my recollections of that visit was that we were able to locate only one Macintosh in the whole company. The other was the enthusiasm with which the chemists embraced the ChemDraw application. In the following months Lilly ordered dozens of Macs as a consequence of the rapidly growing enthusiasm among its chemists for this software.

Beta Testing ChemDraw

By personal decree, my research group bent to the pressure of becoming the principal beta test site for the program, and in 1986–1987 the first of five PhD theses were written with the aid of ChemDraw (CD). During this period I had approximately 22 co-workers, and the combined involvement of mentor and students was intense. These were trying times! For example, when one was working with CDβ-0.48, if that software version “locked up” one could not re-access the CD file under construction with an earlier version of the software (CDβ-0.47). Consequently, the student had to pause

until (CDβ-0.49) was installed to complete the scheme that had been “held hostage”. This drove everyone to distraction as they were invariably subject to deadlines to deliver their theses. In order to avoid personal injury, Stewart developed the habit of updating the software at least once a day, preferably late in the evening. I recently contacted Kevin Chapman to ask him for some of his memories of the ChemDraw experience. He responded, “Do you want quotes or epithets!”^[18] I had not anticipated these problems, and had some fence-mending to do with my group.

Incorporation

In 1985 Sally introduced Stewart to a law firm to represent his interests at the Harvard Technology Transfer Office. Harvard subsequently ruled that there had been no valid challenge to Stewart's claim to be the inventor of the program that is now called ChemDraw. In 1986 Cambridge Scientific Computing was launched. Stewart noted that, “the name was changed to CambridgeSoft some years later when another, larger corporation, CSC (Computer Sciences Corporation), objected to the use of those initials.” It is of historic interest that the first person to purchase a ChemDraw license was Stuart Schreiber, then an Assistant Professor on the Yale faculty. I had alerted Stuart to the existence of this program, and he had seen what the early versions of the program could deliver. Stuart became an early participant in the beta testing effort. I recently shared a draft of this Essay with him. His response was, “*Thank you sharing your fascinating and illuminating Essay on a transformational event in organic chemistry. ChemDraw changed the field in a way that has not been replicated since.*”^[19]

The Corey Connection

There has been considerable speculation within the chemical community as to the origin of the ChemDraw program and who should be credited for this innovation. In retrospective discussions of this sort, history is replete with a litany of claims as to who is the real inventor (or co-inventor) of the concept/application. In the Corey monograph, *The Logic of Chemical Synthesis*,^[20] the authors provided the following statement in the preface:^[21] “*The reaction flow charts of Part Two, and indeed all chemical formulae which appear in the book were generated by computer. The program used for these reactions was ChemDraw adapted for the Macintosh personal computer by Mr. Stewart Rubenstein of these laboratories from the molecular graphics computer program developed by our group at Harvard in the 1960s and subsequently refined.*”

My interpretation of this statement was that Corey viewed Rubenstein's ChemDraw efforts as an extension of his own contributions evolving from the LHASA synthesis design project and by implication, E.J. was at least a partner in this invention. Even though Stewart was a Corey graduate student, the program was developed on Stewart's own time with his own computer. With regard to the Corey ChemDraw

relationship, Stewart states that, “the LHASA group must be given credit for developing the idea of drawing chemical structures on a computer screen. While I was not involved in that development at all, it certainly provided some amount of inspiration and proof of concept. The methods (that) I used for input and output of chemical structures on the Macintosh were, however, all original, distinct, and not derived in any way from the LHASA code.”^[22] While all of this is true, E.J. did create the environment and the expertise to make this invention possible.

In the final analysis, the Harvard Technology Transfer Office ruled that Rubenstein was the sole inventor of the ChemDraw program.

Michael Rubenstein^[23] and Chem3D

The development of the companion three-dimensional structure drawing program, Chem3D, was begun in the latter months of 1985 by Michael Rubenstein, Stewart's younger brother. Michael had recently graduated from Oberlin College and moved to Cambridge to collaborate with Stewart on the launch of Cambridge Scientific Computing and to develop Chem3D. I also worked with Michael on this project as well. My role in these interactions was to suggest advances that might improve the user interface. I cite one instance where I provided feedback: In the selection of a stereoscopic view of a structure, the viewing perspective is most critical. The more overlapping atoms that are present in a given view, the less value it is to the overall structural representation and to the viewer. As an aid to finding optimal viewing perspectives, I suggested that Michael could develop an algorithm that presented those structures that minimized atom overlap for each potential structure. He never did incorporate this suggestion! Such is the nature of any collaboration!

Living with ChemDraw

ChemDraw has fundamentally altered my approach to presenting lectures to the chemical community. In the pre-ChemDraw era, graphics were prepared and then passed along to the photography department to be turned into slides. For this step, a one-week lead-time was advised. When the slides became available, one could then assemble the lecture. In contrast, with ChemDraw and a suitable presentation program, the way lectures can be assembled has changed dramatically. Today, one may complete the presentation an hour before delivering the formal lecture.

In the preparation of this article, I undertook an informal survey of ChemDraw usage for scientific publications in organic chemistry based on the journals *Organic Letters* and *Journal of Organic Chemistry*. For *Organic Letters*, 20/20 manuscripts examined used the indicated software;^[24] for the *Journal of Organic Chemistry*, 19/20 manuscripts also used the same software.^[25] While this is hardly a thorough scientific survey, the data suggest that ChemDraw remains the dominant chemical graphics drawing program used by the organic

chemistry community for the preparation of scientific publications. To date, approximately 1 000 000 licenses have been issued for this application.^[26]

Beneficiaries

Sally and I had no interest in profiting financially from this collaboration. I viewed Stewart as a wonderfully talented student with whom I enjoyed interacting! At the end of this collaboration, I was the beneficiary of a structure drawing program tailored to my professional needs. Sally benefited greatly by no longer having to serve as the group's graphic artist! Finally, Stewart was able to market ChemDraw to the chemical community and to create a viable new company, Cambridge Scientific Computing.^[27] It is a credit to all participants that this software continues to dominate the chemical graphics needs of the worldwide chemical community nearly three decades after its introduction.

Finally, the Harvard Chemistry Department greatly benefited from this collaborative activity. This project signaled that important contributions to the chemical community were continuing to be generated in our department. In any academic environment, one should promote such scientific interactions wherever they arise. I have written this short account to describe the wonderful scientific relationship that I developed with Stewart and Michael Rubenstein during my early days on the Harvard faculty. This collaborative project also provided counterpoint to the long-held rumor that, “the students at Harvard never interact with the other chemistry faculty.”

Epilogue

A relevant announcement from the American Chemical Society has just been released:^[28] “The exciting collaboration combining the familiarity and ease-of-use of ChemDraw with the power and authoritative content of SciFinder has arrived! This landmark collaboration from CAS and PerkinElmer improves your workflow by integrating two of the most popular platforms for scientific research and discovery. Now you can draw structures and reactions in your favorite drawing tool and be taken directly to the relevant search results within SciFinder using the new Search SciFinder button in ChemBioDraw Ultra 14.”

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- [1] S. S. Shaik, P. C. Hiberty, *A Chemist's Guide to Valence Bond Theory*, Wiley-Interscience, Hoboken, **2008**.
- [2] W. O. Kermack, R. Robinson, *J. Chem. Soc. Trans.* **1922**, 121, 427–440. For an overview see: D. O'Hagan, D. Lloyd, *Chemistry World*, **2010**, 7(4), 54–57; S. Alvarez, *Angew. Chem.* **2012**, 124, 610–621; *Angew. Chem. Int. Ed.* **2012**, 51, 590–600.
- [3] I was prompted to introduce this preamble to the Essay since anyone under the age of 50 years was not a practicing chemist in 1986, the year ChemDraw was introduced.

- [4] Leroy Lettering Sets were manufactured by Keuffel & Esser Co. (copyright 1950). These templates have been widely used for inked lettering on architectural and engineering drawings and maps.
- [5] The Chemist's Triangle has been marketed by Sigma Aldrich for at least 50 years. It was a mainstay tool of nearly every student of organic chemistry until the advent of ChemDraw. It has been informally called Fieser's Triangle and will be referred to in this way in this essay.
- [6] For an overview of this workstation see: *Wikipedia*, search term: "Xerox Star." See: <http://www.digibarn.com/friends/curbow/star/retrospect/index.html>.
- [7] http://en.wikipedia.org/wiki/Xerox_8010. The Xerox Star System was technically known as the Xerox 8010 Information System.
- [8] WYSIWYG: is the acronym for "What You See Is What You Get."
- [9] S. W. Evans, A. B. Oberlin College, 1963. Significant teaching positions: Westridge School, Pasadena, CA; Westlake School for Girls, Holmby Hills, CA; Dana Hall School, Wellesley, MA; Belmont Day School, Belmont, MA; Montrose School, Westwood, MA.
- [10] "Macintosh and the 1984 commercial" may be viewed on YouTube. <https://www.youtube.com/watch?v=2zfqw8nhUwA>.
- [11] Kevin Maney, *USA Weekend*, January 28, 1984.
- [12] <http://en.wikipedia.org/wiki/MacDraw> MacDraw graphics are displayed along with the available drawing tools. This was one of the programs supplied with the purchase of the Macintosh computer.
- [13] Stewart D. Rubenstein: intern at SUMEX-AIM (programming) 1978–1979; intern at Hewlett–Packard Life Sciences Group, 1979–1980; B.S. Chemistry, Stanford University, 1980; M.S. Chemistry, Harvard University 1982; President, Cambridge Scientific Computing (later, CambridgeSoft Corp.) 1986–2006. E-mail: stew@stewrubenstein.com.
- [14] LHASA is the acronym for "Logic and Heuristics Applied to Synthetic Analysis".
- [15] J. Brecher, *Pure Appl. Chem.* **2006**, 78, 18971. There are several cases where two wavy lines for a tetrahedral carbon are recommended. See Section ST-0.4 Wavy Bonds.
- [16] Stewart Rubenstein, personal communication, April 17, 2014.
- [17] <http://en.wikipedia.org/wiki/LaserWriter>. The LaserWriter was Apple's first postscript printer. It was introduced in March 1985 at a cost of \$6995. This product was not actually delivered until later in the year.
- [18] Kevin Chapman, personal communication, April 22, 2014.
- [19] Stuart Schreiber, personal communication, April 25, 2014.
- [20] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, Chichester, **1989**.
- [21] E. J. Corey, W. T. Wipke, *Science* **1969**, 166, 178.
- [22] Stewart Rubenstein, personal communication, April 20, 2014.
- [23] Michael C. Rubenstein: A. B. Oberlin College, 1984; Executive Vice-President and Director, Cambridge Scientific Computing, Inc. (later, CambridgeSoft Corp.), 1986–2006; Chief Technical Officer and Director, CambridgeSoft Corp., 2006–2011; Senior Technical Leader, PerkinElmer Corp., 2011; Advanced Leadership Fellow, Harvard University, 2014. E-mail: michaelcrubenstein@gmail.com.
- [24] Clarissa Steinhagen, Managing Editor of *Organic Letters*, personal communication, May 27, 2014.
- [25] Katie Turner, Coordinating Editor of *Journal of Organic Chemistry*, personal communication, May 27, 2014.
- [26] Hans Keil, Director, Academic Market Segment, PerkinElmer Informatics, personal communication.
- [27] Cambridge Scientific Computing was incorporated in January 1986.
- [28] Craig Stephens, personal communication. See What's new in SciFinder: <http://www.cas.org/products/scifinder/what-s-new-in-scifinder>.