centers. As explained above, the dissociation of the bond between the η^2-2,2′-bipyrimidyl ligand and the Pt^{II} center is reversible. The question may be raised whether the ligands are bonded to the Pt center during the transition state. As metal salts also catalyze the reaction—however, with lower activity and selectivity—the ligands must be relevant for the selectivity of the reaction.

How is the high selectivity of the process achieved? According to Periana et al., the rate constant of the oxidation step of CH_4 to methyl bisulfate is 100 times higher than that of the further oxidation of methyl bisulfate.[13] Methanol can be trapped by esterification and thus be protected from nonselective consecutive reactions. Therefore, only low amounts of CO_2 and traces of methyl chloride are formed. This appears to be the key towards high selectivities. A similar concept also enables high selectivities when methane is activated by super acids (Table 1): The selective products are trapped after protonation as $[CH_3OH_2]^+$ or $[CH_3O]^+$.[9] With catalyst **1**, space time yields of $10^{-6}\,mol\,cm^{-3}\,s^{-1}$ (ca. $0.1\,t\,m^{-3}\,h^{-1}$) are obtained. This makes the process interesting from a technical point of view. Whether such a process can be applied technically depends on the long-term stability of the catalyst. From the given turnover numbers and frequencies, a time span of 14 hours can be calculated during which the catalyst is completely deactivated. This shows that further improvement is necessary. Furthermore, when evaluating the process efficiency, the necessary workup steps—hydrolysis of the ester, destillation of methanol, oxidation of the formed SO_2 to SO_3 (space time yield $0.2-0.2\,t\,m^{-3}\,h^{-1}$) for regeneration of sulfuric acid as oxidizing agent—have to be taken into account.

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Large Molecules from the Virtual Bakery—Filling a Gap in Structure Research**

Peter Luger*

It is a common practice for preparative chemists to cook or bake their new compounds in hot ovens. By contrast, the determination of the structure of large molecules by "shake-and-bake" (or half-bake) in the gigabyte world of modern computers is a new, but very successful, method and fills a long-lamented gap in the otherwise very effective field of structure research by X-ray diffraction. When the Japanese group of Kondo et al.[1] solved the crystal structure of the deep-blue flower pigment commelinin six years ago, it caused such a sensation that this compound was featured on the cover of the first August issue of *Nature*. The group was also awarded the prize for the best poster contribution at the 16th International Crystallography Congress in Beijing in 1993.[2] The scientific community is used to the scientific literature being expanded through the addition of routine crystal structure solutions, so why was this particular one so special? One aspect may have been its aesthetic value, for the commelinin structure (Figure 1, top) is almost as beautiful as the flowers from which it is derived.

But there is more to its significance than just good looks. It contains 253 non-hydrogen atoms in the asymmetric unit and thus belongs to that group of middle-sized structures that were formidable tasks for crystallographers to solve in the early 1990s. The number of structures registered at the Cambridge Crystallographic Data Centre (CCDC) has increased almost exponentially for thirty years, with more than

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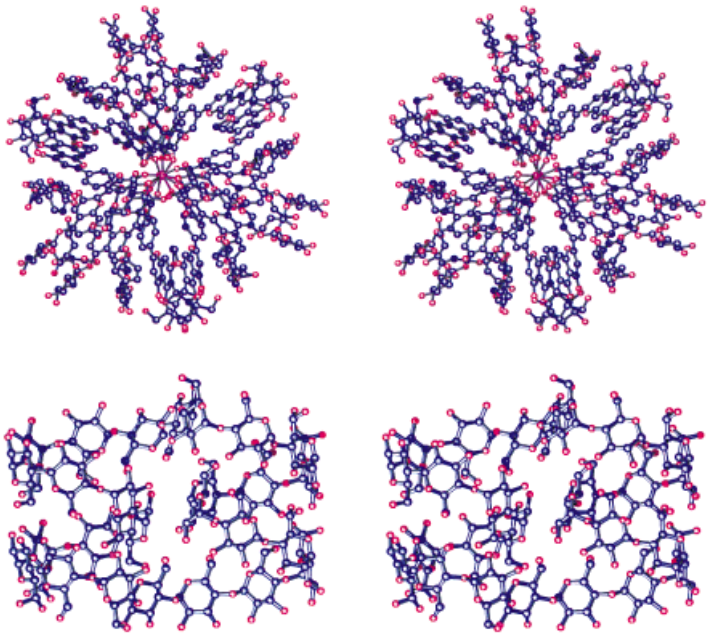

Figure 1. Top: Structure of the flower pigment commelinin[2] that was solved in the early 1990s by classical direct methods; bottom: structure of a cycloamylose[22] that consists of 26 glucose units and is one of the largest light-atom structures of atomic resolution solved by SHELXD. Both stereo figures are plotted with the program SCHAKAL.[30]

10000 new structures each year. The Brookhaven Protein Data Base has been through a similar development lately with about 1000 new structures each year (Figure 2). This progress

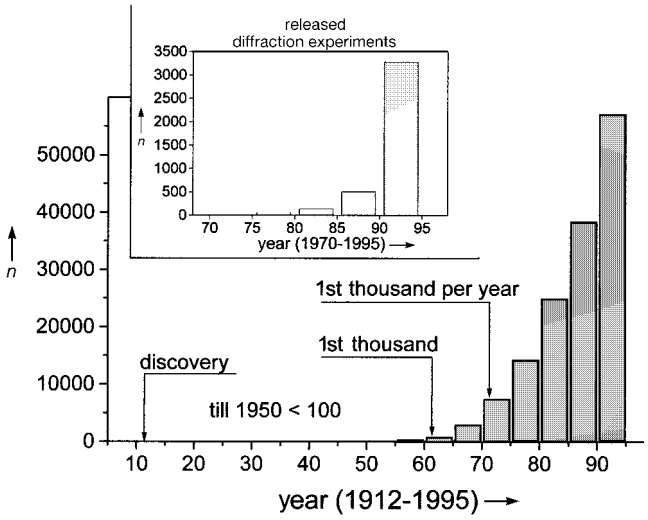

Figure 2. Number n of entries into the Cambridge Data File in the Cambridge Crystallographic Data Centre (CCDC) shown in five year intervals. The insert shows the corresponding entries into the Brookhaven Protein Data Bank (1970–1995).

has taken place with small structures, where the limit was first about 100 atoms and then increased to nearly 200 non-hydrogen atoms, and with protein structures of molecular weights in the kilodalton range. Structures with several hundred atoms in the asymmetric unit have remained difficult to solve. Among the purely organic structures stored in the Cambridge Data File fewer than 300 entries have more than 100 carbon atoms in the formula and only 16 entries have more than 200 carbon atoms.

In the April 1992 "Research News" article in Science[5] the author described the situation of the in-between molecules—those having between 200 and 500 atoms—in familiar terms: "In large families, the oldest child and the youngest often get most of their parents' attention, while the middle children seemingly get lost in the crowd". Actually, crystallographers cannot be called negligent parents. The reasons for their lack of attention have been serious. One problem is the difficulty with the crystallization of middle-sized compounds, because as the bulk increases the propensity to crystallize greatly diminishes. At the other end of the size spectrum, the very large structures, such as proteins, form less flexible and more globular molecules and tend to crystallize again better than the in-between ones. It also has to be added that a great deal of research effort, including trials in outer space, has been invested in the crystallization of macromolecules.[6]

A further problem is that the otherwise so effective "direct methods" for solving the crystallographic phase problem fail for the in-between molecules and that the methods usually employed for protein structures are not yet applicable. Thus, hardly any usable methods have been available for the determination of these middle structures. Hence, when one of them could be solved the success commanded a great deal of attention, as with the commelinin example.

Recently, two actinomycin structures were published by Sheldrick et al. [7] in *Angewandte Chemie* (actinomycin D and Z_3, with 314 and 307 atoms in the asymmetric unit, respectively), which indicates that the gap can now be closed if intensity data of atomic resolution (that is, down to about 1 Å) can be collected. However, methods with new strategies had to be developed. One source of such innovation was, once again, Herbert Hauptman, one of the fathers of direct methods, and the recipient of the 1985 Nobel Prize for chemistry, which he shared with Jerome Karle for their pioneering work in this area. In 1988 Hauptman introduced the minimal function $R(\varphi)$[8] in which a central role is played by the three- and four-phase structure invariants, the triplets $(\varphi_{hk} = \varphi_h + \varphi_k + \varphi_{-h-k})$ and quartets $(\varphi_{lmn} = \varphi_l + \varphi_m + \varphi_n + \varphi_{-l-m-n}$, where h,k,l... are reciprocal lattice vectors of Bragg reflections), which were known from classical direct methods. For the triplet and quartet relationships (more exactly, for $\cos\varphi_{hk}$ and $\cos\varphi_{lmn}$) the expectation values ε_T and ε_Q, respectively, can be calculated, and the minimal function $R(\varphi)$ is thus expressed by Equation (1).

$$R(\varphi) = \frac{\sum_{h,k} A_{hk}[\cos\varphi_{hk} - \varepsilon_T]^2 + \sum_{l,m,n} |B_{lmn}|[\cos\varphi_{lmn} - \varepsilon_Q]^2}{\sum_{h,k} A_{hk} + \sum_{l,m,n} |B_{lmn}|} \quad (1)$$

Hauptman also introduced the minimal principle,[9] which involves the minimization of $R(\varphi)$, and leads to a set of phases of the correct structure.[10]

The practical implementation of the minimal principle is the "shake-and-bake" algorithm and computer program.[11–13] It differs from the classical direct methods programs, which operate only in reciprocal space, in that during each of its cycles shake-and-bake carries out calculations alternately in reciprocal and direct space: This procedure automatically

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takes account not only of the condition that the correct structure has positive electron density everywhere, but also of the fact that sharp local electron density maxima should appear that correspond to atomic positions. The atomicity of a chemical structure thereby enters the calculations directly.

Shake-and-bake is executed in several steps that alternate between direct and reciprocal space,[14] (Figure 3). First, a random test structure is generated in real space, whose Fourier transformation provides structure factors and hence

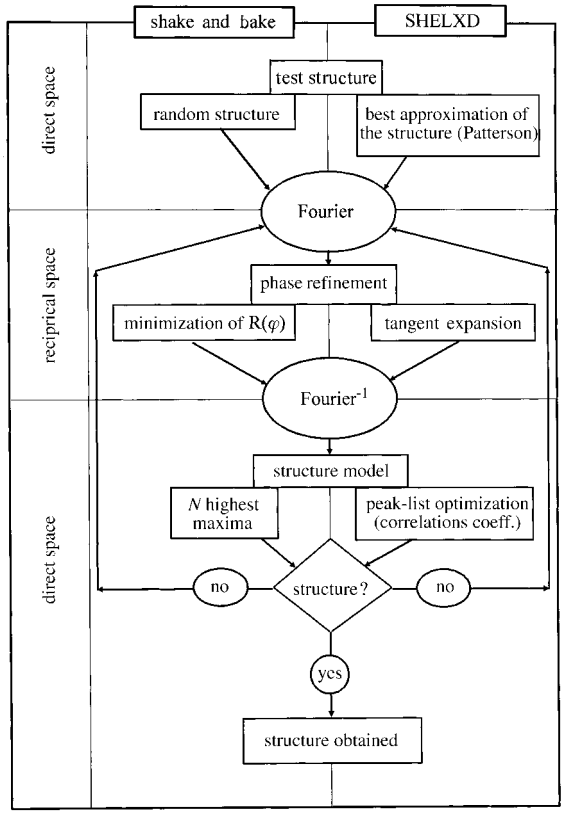

Figure 3. Schematic representation of the algorithms of shake-and-bake (left) and of SHELXD (right).

also starting phases in reciprocal space. This is the "shake step" of the procedure. Through phase refinement by iteration, the minimization of $R(\varphi)$ is attempted. After this cycle of minimization a new structure is "baked" by calculating an electron-density map in direct space with the now supposedly improved phases. The N highest maxima of this map is considered to be the new set of atoms, and the phases derived from them by another Fourier transformation, the next "shake step", give a new set of phases to be improved by phase refinement in reciprocal space.

This procedure usually has to go through several hundred shake-and-bake steps until it can be recognized from the trend of $R(\varphi)$ whether it converges to the correct structure. One test structure alone usually leads to a false minimum rather than to the desired result. Therefore, several thousand trials are carried out, each with another random starting set.

Inspired by shake-and-bake, George Sheldrick has developed SHELXD [15, 16] a program especially designed for the solution of structures in the 200–2000 atom range. The similarities and differences of the two methods can be seen in Figure 3. Sheldrick tries to dispense with the random starting structures. For instance, if a heavy atom is present in the structure he applies an ingenious Patterson interpretation[17, 18] routine at the outset. This approach makes the phases of the starting set more reliable than they are in a completely random structure. A conventional tangent phase-refinement is then applied, and an inverse Fourier transformation results in a new structure model. The highest N maxima are not selected automatically as input atoms for the further course of the process; instead a peak-list optimization[19] is initiated. Starting with the lowest peak the maxima are individually evaluated for their acceptability as atoms. This decision depends on whether the presence of a peak improves or worsens a correlation coefficient introduced by Fujinaga and Read in 1987.[20] A carefully screened atom list is thereby introduced into the next cycle.

By means of this peak-list optimization (and the possible Patterson evaluation at the beginning) SHELXD works with higher weight in direct space than shake-and-bake does. For some time Sheldrick himself called his method "half-baked",[19] but in view of the successes of the method, one could now call it "fully baked". In addition to the above-mentioned actinomycin structures, several others that were previously considered unsolvable, have been elucidated with SHELXD. Examples are vancomycin,[21] an important antibiotic with 313 independent (non-hydrogen) atoms in the asymmetric unit, and a cycloamylose consisting of 26 glucose units and having almost 650 atoms (two molecules in the asymmetric unit).[22] The latter long held the record as the largest light-atom structure determined with atomic resolution (Figure 1, bottom). This structure is surpassed by the present "world-record holder", the lantibiotic mersacidin,[23] whose size of 850 independent atoms corresponds to a protein with a 120 amino acid sequence. Somewhat outside this competition, since it was known before, is the triclinic structure of HEW-lysozyme (Figure 4), which was redetermined by the Sheldrick group, and exceeded the 1000-atom limit for the first time![24]

Given that several hundred cycles have to be calculated for one trial and several thousand trials have to be run for a structure determination, the computer time required for the methods discussed here may be expressed in VAX years.[19] Because VAX computers were the usual computing tools in chemical laboratories in the 1980s, neither shake-and-bake nor SHELXD would have been possible to run, even if these algorithms had already been worked out. Today's processors have increased the computing speed by two orders of magnitude, which reduces the computing time of VAX years to an acceptable number of hours or days. Because the new algorithms need data sets with atomic resolution, these methods could hardly have succeeded without the remarkable progress that has taken place in the experimental field in recent years, especially the new developments in crystallization techniques[25] and the improved possibilities for X-ray data collection. By using synchrotron radiation, possibly with the crystal samples kept at low temperatures, one can greatly improve the ratio of reflection intensity to background,

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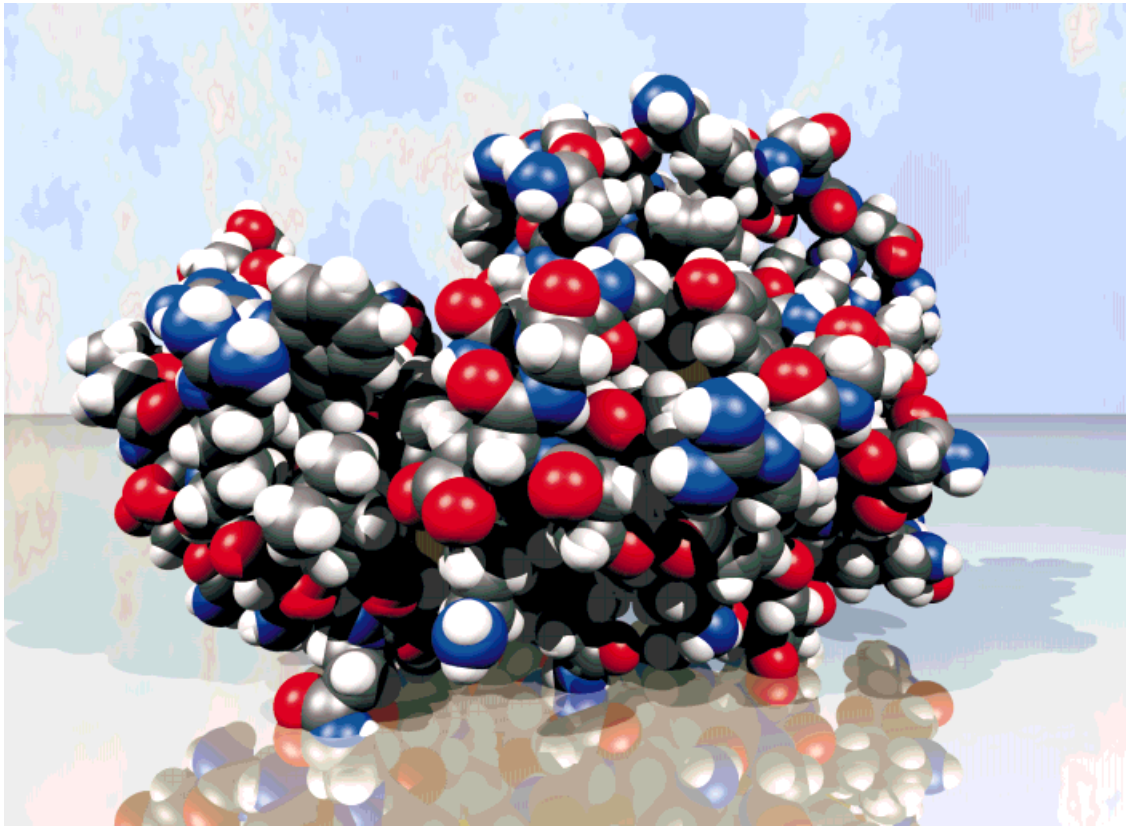

Figure 4. The 1001 independent atoms in the structure of the triclinic form of HEW-lysozyme.[24]

especially in high-angle ranges. If this radiation is combined with area detectors, such as the new CCD systems (for example the SMART-diffractometer,[26] which appeared on the market in April 1994), then not only the resolution increases, but also the speed of the data collection is enhanced by several orders of magnitude[27] relative to that of usual diffractometers with serial counters and conventional X-ray tubes, which is a very significant factor in the case of large structures. Through these developments—as in the 1960s—another great surge in innovations has taken place in crystal structure analysis, a leap propelled by concurrent breakthroughs in theory, experiment, and computer technology. It seems that the gap in the elucidation of molecules that contain several hundred atoms may close before the end of this century.

Modern chemistry offers numerous problems to solve. Only in the class of naturally occurring antibiotics or cytostatics, whose increasing importance has recently been emphasized in the highlight article by Lindel,[28] are there various molecules of several hundred atoms each. The solution of one of these has been until now, the exception,[29] but henceforth the chances of their successful X-ray structure determination are very good indeed.

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Deposition of Data from X-Ray Structure Analyses

In order to make life easier for authors and referees the Cambridge Crystallographic Data Centre (CCDC) and the Fachinformationszentrum Karlsruhe (FIZ) have unified their procedures for the depostion of data from single-crystal X-ray structure analyses.

Prior to submitting a manuscript please deposit the data for your compound(s) **electronically** at the appropriate date base, that is, at the CCDC for organic and organometallic compounds and at the FIZ for inorganic compounds. Both data bases will be pleased to provide help (see our *Notice to Authors* in the first issue of this year). In general, you will receive a depository number from the data base within two working days after electronic deposition; please include this number with the appropriate standard text (see our Notice to Authors) in your manuscript. This will enable the referees to retrieve the structure data quickly and efficiently if they need this information to reach their decision.

This is now the uniform procedure for manuscripts submitted to the journals *Advanced Materials, Angewandte Chemie, Chemistry—A European Journal,* the *European Journal of Inorganic Chemistry,* and the *European Journal of Organic Chemistry.*

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