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Solutions for chemistry: synthesis of experiment and calculation

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THE ROYAL SOCIETY

Solutions for chemistry: synthesis of experiment and calculation

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Making molecules is fundamental to the development of all new substances, including new materials and health products. Organic synthesis is engineering on an atomic scale, and requires techniques of mass production so that it is possible to make copies of molecules not just in hundreds or thousands, but in billions of billions of billions. As a result, organic synthesis is an extremely demanding discipline, requiring both a wide knowledge of chemistry and also the ability to develop complete strategies for the construction of molecules. If the last step of a synthesis does not work, then it may be necessary to begin again by altering the first step. Organic synthesis is sometimes compared with a game of chess, where the effects of the opening moves are felt right through to the end game, and where the number of possible situations is greater than can be comprehensively analysed by any computer.

Chess, however, is succumbing to computers. Only the very best human chess players can compete on a level with the best chess-playing computers, and every year the computers become more powerful. It is unlikely that the chess champion of the world will be human for any of the third millennium. The best designers of organic syntheses are unquestionably human, at the end of the second millennium. For how much longer will this pre-eminence continue?

Quantum mechanics gives a good understanding of how molecules behave, but the calculations required are much too time consuming for Schrödinger's equation to be able to compete with the best organic synthetists. Information technology enables computers to know the chemistry literature better than any person, but this, in itself, is not sufficient to design syntheses of new compounds. The use of these two approaches together, however, may enable computers to design better syntheses. The development of the World Wide Web has shown that it is possible for computers to communicate on a global scale, and this, coupled with developments in theoretical chemistry, may lead to computers making useful contributions to synthetic strategies in the near future.

This article gives a brief history of organic synthesis, highlighting the issues that make this such a demanding subject. It also sketches the development of quantum theory, as applied to chemistry, and information technology tools. These techniques are just reaching the stage at which they may be able to interact constructively, and so solutions for chemistry may be available early in the new millennium.

Keywords: organic synthesis; computer-aided organic synthesis (CAOS); molecular modelling; chemoinformatics

Making molecules has been important to human society from prehistoric times. The extraction of tin and lead from their ores has been possible for thousands of

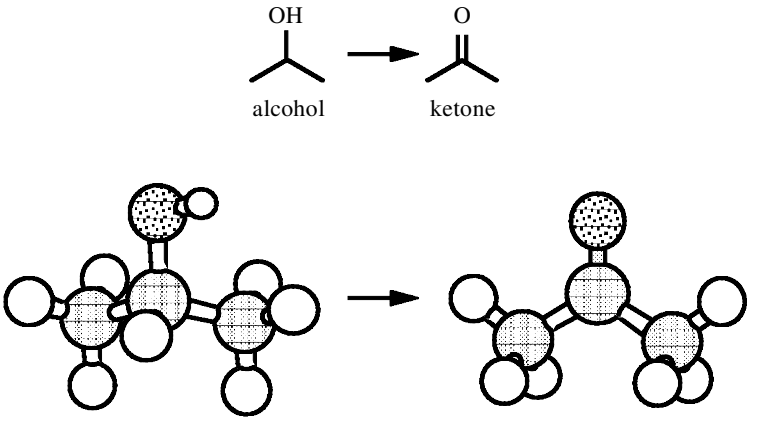

Figure 1. The transformation of an alcohol to a ketone. The stick drawings at the top show the same molecules as the alternative representations below. In the lower version, hydrogen atoms are white, carbon atoms are dark grey, and oxygen atoms are speckled. The hydrogen atoms attached to carbon are omitted from the more concise representation at the top. Many reagents are available that will transform an alcohol into a ketone.

years. Fermentation has also been controlled to produce alcohol for millennia. In the last century, carbon-containing molecules have become increasingly important for the development of new substances, including plastics, other new materials and health products. Organic chemistry was originally the study of compounds connected with life, but, more than a century and a half ago, Wöhler showed it was possible to make an organic compound (urea, which may be extracted from urine) from inorganic (that is, non-living) compounds. What had seemed a precise distinction between living and non-living compounds became hazy. The subject may now be defined as the study of molecules that contain carbon atoms, although the precise boundaries of the area are not clear: the overlap with biology, with materials science, with inorganic chemistry, and with physics can all be debated and boundaries drawn and redrawn. However, it is clear that the understanding of organic chemistry advanced tremendously in the closing century of the second millennium.

Increasing knowledge of the properties of molecules has made it possible to synthesize very complicated compounds. Organic synthesis is engineering on an atomic scale, and requires delicate operations to be performed on objects that are too small to see. It also requires techniques of mass production, because single molecules are usually not useful by themselves. A car factory may produce tens of thousands of cars each year, but this is very small scale compared with the job of a synthetic chemist. A pint of beer contains approximately 10^{25} (ten million million million million) molecules. If you were to pour a pint of beer into the sea, wait for the waves to mix it well all around the world, and then take a pint of seawater from any part of any ocean, that pint would probably contain a thousand molecules from the original pint. A successful synthesis of a new molecule would not make hundreds or thousands of copies of the molecules, but millions of millions of millions. For this to be possible, every step of the synthesis must work well.

In order to make a complex molecule, it is necessary to have methods that join simpler molecules together, and also techniques to make small changes to different bits of the molecule, once the framework has been constructed. There is an enormous

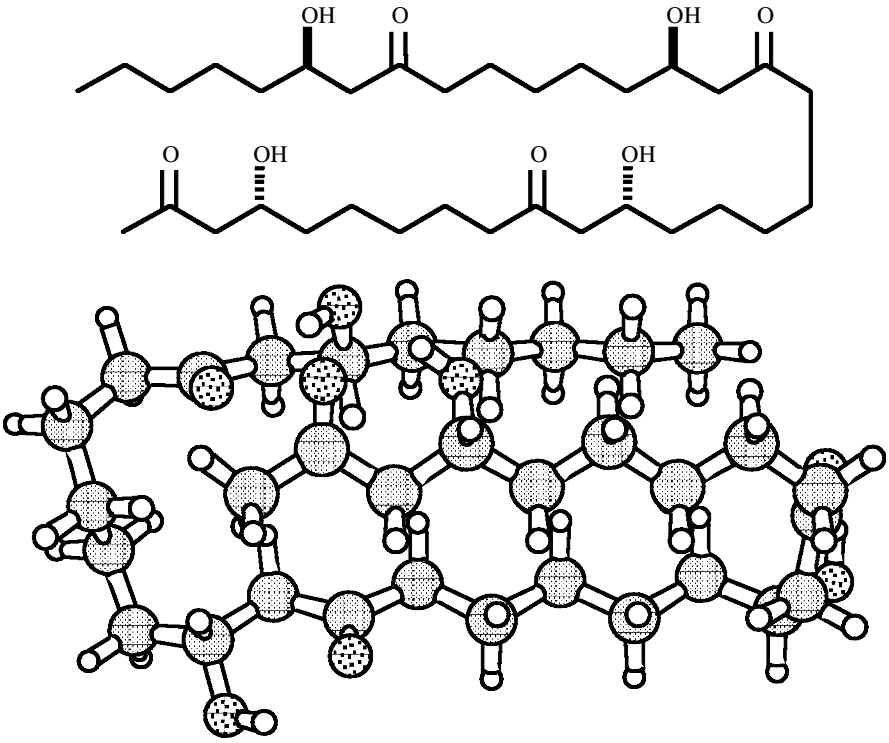

Figure 2. PM-toxin A (Hayakawa *et al*. 1997). This molecule, which is produced by the fungal pathogen *Phyllosticta maydis*, was the cause of major epidemics of leaf-blight disease in the US. The molecule is toxic only to specific plants. The lower illustration shows a low-energy conformation of the molecule.

variety of reagents that can be used to transform one arrangement of atoms into another. A common transformation is to turn alcohols into ketones (figure 1). Every reagent that is added will act on the whole molecule. This is not a problem for the structures illustrated in figure 1 because there is only one alcohol group in the starting material and so all of the alcohols are transformed into ketones. It is a problem if the same transformation is used to make a more complicated molecule, such as PM-toxin (figure 2). In this molecule there are several alcohols and several ketones. A synthesis could not finish by oxidizing just some of the alcohols to ketones, because the reagent would not know which alcohols should be oxidized and which should not. This is a major problem for synthesis. How is it possible to selectively make ketones in the presence of alcohols? More generally, how can a transformation be made to act on only a part of a molecule?

Two general approaches can be used to find solutions to this problem. Selective reagents could be developed, so that it is possible to change some alcohols into ketones without affecting others in the same molecule. For example, the lower left-hand ketone in PM-toxin is close to the end of the carbon chain. Might it be possible to develop a reagent that only oxidizes alcohols that are close to the end of carbon chains? An approach of this sort would require a very good knowledge of the properties of reagents. Alternatively, a strategic approach could be tried. The molecule

could be joined together in such a way that the question does not arise, because the alcohols and ketones are already in the right places as a result of the choice of joining processes. In practice, a combination of these methods may be required in order to make complex molecules.

As a result, organic synthesis is an extremely demanding discipline, requiring both a wide knowledge of chemistry and also the ability to develop complete strategies for the construction of molecules. If the last step of a synthesis does not work, then it may be necessary to begin again by altering the first step. Dr Who, the science fiction character, has machines that can synthesize molecules just given the target structure. Might it be possible to build such a machine? The physical manipulations of mixing and purifying compounds can be automated to a large extent, and it is possible to imagine building a machine that could do the mechanical tasks of a highly trained synthetic chemist, although it would be far more expensive and probably less effective than a skilled individual. The main difficulty in the construction of such a machine would be to provide the machine with suitable instructions for the synthesis.

Organic synthesis is sometimes compared with a game of chess, where the effects of the opening moves are felt right through to the end game, and where the total number of possible situations is greater than can be comprehensively analysed by any computer. Chess games require an opponent, whose responses to the strategy chosen by the opening moves determine the course of the game. Organic synthesis may be regarded as a similar challenge. A good chess player may reasonably be expected not to make a foolish response to any situation that is presented, but the details of the response are not predictable. The same is true of organic synthesis, contending with the properties of molecules. Organic reactions are well understood, but if a reaction is performed in a completely new context, then the molecule's response may not be exactly as expected from the experience gained through earlier studies of related systems. The variety of possible responses makes chess a demanding game, and organic synthesis a challenging subject.

Chess, however, is succumbing to computers. Only the very best human chess players can compete on a level with the best chess-playing computers, and every year the computers become more powerful. It is unlikely that the chess champion of the world will be human for any of the third millennium. At the end of the second millennium, the best designers of organic syntheses are unquestionably human. For how much longer will this pre-eminence continue?

A molecule-building computer would need to understand chemistry. This is possible. Quantum mechanics provides a method for calculating how molecules behave with a high level of precision, using Schrödinger's equation. Dirac (1929) wrote:

> The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.

Since that time, advances in computers have made some of these complicated equations not only soluble, but routinely used. However, the equations become more complicated very rapidly as larger systems are considered, and so the exact application of these laws remains out of reach, except for the smallest molecules. Many useful approximations have been developed in order to extend the range of possible

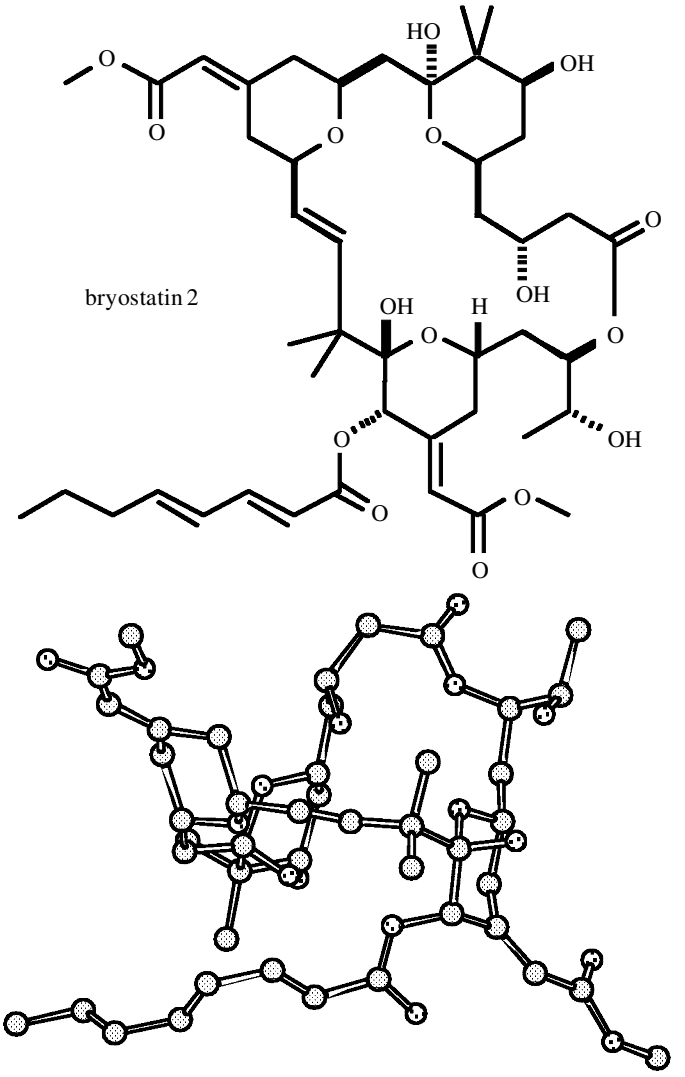

Figure 3. Bryostatin 2. In this diagram, all of the hydrogen atoms are omitted in order to simplify the structure. The lower diagram shows a low-energy conformation of bryostatin 2, but it may only be a local minimum and not a global minimum. Many other conformations are accessible at room temperature. Bryostatin ($C_{45}H_{66}O_{16}$) is a biologically active marine natural product, which may have useful anti-cancer properties. It has recently been synthesized at Harvard (Evans *et al.* 1998).

calculations, and the effects of these simplifications are now well known. The 1998 Nobel prize in chemistry was awarded to Pople and Kohn for the development of methods for calculating chemistry.

Solving quantum mechanical problems is a conceptually straightforward way of solving organic chemistry. The problem is simply one of computer power. In order to calculate the energy of a molecule the size of PM-toxin (figure 2) or bryostatin (figure 3), an extremely complex calculation must be done, but it is now possible to

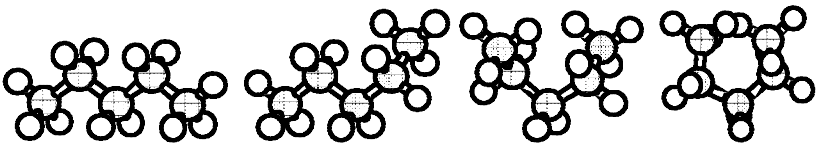

Figure 4. Pentane. The diagram shows the four minimum-energy conformations of pentane. The global minimum is on the far left. Reflection and rotation of some of these geometries would generate more structures, but nothing with a different energy.

do this using advanced quantum chemistry programs. If lower accuracy is acceptable, then the calculation may even be made easy using the much greater approximations of force fields. Once the energy has been found, it is possible to calculate the preferred shape of the molecule, by finding alterations to the shape of the molecule that lower the total energy. This process of altering the structure and recalculating the energy is continued until all small changes to the structure lead to an increase in energy. The shape that the molecule has now reached is called a minimum-energy conformation. This requires many calculations of the energy of the structure.

This does not, however, solve the problem of synthesis. A minimum-energy conformation is the lowest energy point in the immediate vicinity, but it may not be the lowest energy geometry available to the molecule. The lowest energy point of all is called the global minimum. There can only be one global minimum for any molecule, but there may be very many local minima. These are geometries for which any small change will increase the energy of the structure, but for which larger changes may lead to a decrease in energy, so they must be higher in energy than the global minimum. This can be compared with a mountainous landscape. Only one point can be the lowest point of all, the global minimum, but there may be many points from which every direction you choose to walk will be uphill.

For a molecule containing several alcohol groups, some conformations may have particular alcohols tucked into the centre of the molecule. This may be helpful, if it means that these alcohols will not react, and others in the molecule may do so. But will each conformation be accessible? One way to assess this is to make a list of all the minima on the surface, and to examine the properties of each. The higher-energy minima will be less likely to be occupied than the lower-energy minima, and this difference can be quantified. This process, called conformation searching, requires many minimizations, each of which requires many energy calculations, and so multiplies the total time required for the analysis. This leaves out all of the parts of the landscape between the minima, and this can be a problem. There are ways of taking these into account, but they are even more time consuming.

A simple molecule is illustrated in figure 4. This is pentane, a chain of five carbon atoms, with hydrogen atoms ensuring that each carbon makes four connections to its surroundings. Pentane has four minimum-energy conformations, as illustrated. The conformation analysis is straightforward, but pentane is a simple molecule. It is not easy to assess accurately the number of conformations accessible to PM-toxin, but the answer is certainly well into four figures, for structures within a few tens of kilojoules of the global minimum. For bryostatin, there are probably many more accessible conformations. Simply being able to calculate the energy of one of these molecules is a long way from understanding its structural properties, which will require many energy calculations.

In addition to finding the minima for each intermediate in a synthesis, it is also necessary to be able to analyse reactivity. This is a more difficult problem than conformation searching, because now it is possible for bonds to break. The range of movements available to the molecule is far larger, and it is also necessary to consider which bond will break most easily, and what factors are present that will drive the reaction forwards. If there are many competing reactions, then these calculations may have to be very precise, in order to distinguish between them.

This problem is made easier because the different reactions have similar starting points, so the question of the most favourable reaction only requires the comparison of similar systems, and this is a great advantage. It is easy to compare two pieces of string to find which is longer, but only if the strings have similar conformations. If one is straight, and the other tied in knots, it may be very hard. Even if both strings are untangled, then it may still be hard to decide which is longer, if they have very similar lengths. Comparing possible reaction pathways is usually like comparing two pieces of string that are both untangled, or, at least, tangled in much the same way. However, the energy differences between processes may be very small compared with the total energy of the system, and so it may be hard to decide which will be preferred.

Analysing structure, conformation and reactivity means that the molecules' reactions, or the opponent's move, may reasonably be predicted for each possible reaction, but such a calculation will be very difficult. Even if we assume that this problem is solved, to a sufficient extent for useful answers to be obtained, then the problem of designing a total synthesis is still not complete.

Molecules such as bryostatin are synthesized by joining together small fragments. How many ways can the fragments be joined together? If we assume that we can buy any molecule with four carbon atoms or fewer, which is a crude approximation, bryostatin (figure 3) will require about ten joins, which suggests that there are ten factorial (three and a half million) strategies to consider. In practice, the problem is not so straightforward, because many different starting molecules could be considered, and the adjustments between alcohols and ketones, and similar transformations, mean that it is necessary to consider many, many times this number of steps. Two steps for each join might be a more realistic estimate of the number of steps expected, so the number of possible approaches is closer to 20 factorial, which is more than a million million million. Each of these strategies will require the calculation of the outcome of many reactions, as outlined above, and each of these calculations is demanding by the standards of the fastest computers available today. A complete solution would not be made possible by an increase in computer power of an order of magnitude, nor by many orders of magnitude.

Several orders of magnitude increase in computer power would be useful to make the calculation of an individual structure rapid, rather than a major project (for molecules of this size). The conformation-searching problem then requires that many such calculations are performed. To analyse reactivity, many competing reaction processes must be considered in order to determine the best conditions for a particular transformation. Many reagents should be considered for each transformation. There are millions of potential transformations that need to be considered in order to fully analyse competing strategies for synthesis. To complete these calculations in a reasonable amount of time—which is to say, faster than a synthesis could be accomplished by expert organic chemists without all of this computational help—will

require much faster computers than are currently available. These calculations will generate an extraordinary quantity of information, which will all need to be analysed. Computers are becoming more powerful very rapidly, but will they become more powerful by a sufficient amount for this problem?

We can obtain a crude estimate of the time required for a precise quantum mechanical calculation to analyse possible syntheses of bryostatin. First, the calculation of the energy of a molecule of this size will take hours. Many such calculations will be required to minimize the energy of a structure. A reasonable estimate may be that a thousand energy calculations would be required. Conformation searching will require many such minimizations, perhaps ten thousand. The reactivity of each intermediate will require a harder calculation, perhaps a hundred times harder. Each step will have many possible combinations of reagents, temperatures, times, and so on. This may introduce another factor of a thousand. The number of possible strategies was estimated before as about a million, million, million. In order to reduce the analysis of the synthesis to something that could be done in a coffee break then, computers would be required that are 10^{30} times as powerful as those available now. This is before the effects of solvents are introduced into the calculation.

Dr Gordon E. Moore (the co-founder of Intel, the computer-chip company) predicted that computers would double in power about every two years, without increasing in price. 'Moore's Law' has held good for almost 30 years. If Moore's law continues to hold true, it will be 200 years before it is possible to analyse a synthesis in a coffee break, and then begin to think about solvents. Moore's law is based on the idea that it will be possible to double the density of components on computer chips every two years. If this is to continue for the next two centuries, it will be necessary to have circuits very much smaller than atoms! It is unlikely that Moore's law will continue to hold for so long. The estimate of the time required is a crude one, and algorithmic advances will undoubtedly play a part in making the problem easier, but it will certainly be a long time before computers can conquer synthesis by brute force.

Can computers, therefore, have any hope of being competitive with people at synthesis, or will people maintain supremacy over machines for the foreseeable future? Fortunately for computers, there is another approach to solving the problem of chemistry. In the introduction to his book, *The nature of the chemical bond* (Pauling 1945), Pauling gives his opinion that it should be possible to describe structural chemistry in a satisfactory manner without the use of advanced mathematics. Books such as this have probably been more influential in the development of modern chemistry than the direct application of quantum mechanics. A computer may do better to read Pauling than to solve Schrödinger if it wishes to contribute to the development of chemistry.

A huge amount of information has been built up by chemists over the last century that is directly useful for solving new problems in organic synthesis. The difficulty lies in retrieving the right information to help with a specific problem. This may simply be finding one piece of information, for example, a particular reaction that has already been done in a similar way, or it may be finding two or more disparate pieces of information that add together to give a better knowledge of what may happen in a new reaction. The advantage of having a large amount of data at the disposal of chemists is also a problem. How can these data be handled effectively?

The textual content of chemistry papers can easily be held in a database, and searched for key words. More sophisticated procedures may also be used, to search for groups of words that tend to appear close to each other, so enabling relevant papers to be discovered. However, chemistry papers are written in many languages and even chemical names are not used consistently. The international language of organic chemistry is structures, such as those drawn in the figures in this article, and these contain more information than can easily be manipulated in words. In the last few years, computers have become sufficiently powerful that an ordinary desktop machine can draw chemical structures, and be used to search a database of structures. This has revolutionized the way that the chemical literature is used. Instead of having to translate a structure to a name and then search a printed index of chemical names in order to find references to abstracts of papers, it is possible to sketch the structure, or transformation, of interest and be presented with an abstract, or a diagram, or even the full paper that uses the structure.

Such techniques mean that the chemical literature may be used more effectively, and that its use can be partly automated. Might this lead to a way of automating organic synthesis? There are many strategies that may be successful in making most molecules. If each reaction of each strategy can be evaluated for similarity to a reaction recorded in the literature, it should be possible to develop a route to most molecules by mechanically searching the chemical literature, so that suitable precedent is found for every transformation.

There are two difficulties with this approach. First, there is the problem of performing all of the necessary searches. As discussed above, there may be billions of possible strategies for making a new molecule. Each reaction in each strategy must be compared with the literature in order to discover if similar reactions have been done before, and if the possible side reactions that could occur are unlikely to do so. This is an enormous task. So much information is available that each search would take a significant length of time. The task is made easier, but less reliable, because much information is not available in a computer-readable form, but, despite this, the time for each search is significant, and there are a great many searches to do. It is also possible that a key reaction has been performed in the past, but was not included in the available online databases, or else that an erroneous result is recorded as if it were true.

Second, it is hard to define similarity in this context. A synthesis may require the transformation of an alcohol to a ketone, and there is ample literature precedent for this. But if there are other alcohols in the molecule, or other groups of atoms that may be affected by the same conditions, it may not be possible to establish this from the literature. If an alcohol is in an unusually crowded position, it may be rather hard to change it into a ketone. Literature precedent may include some crowded alcohols, but nothing quite as crowded, or nothing quite as crowded in the same way. This may be because nobody has tried a similar reaction, or it may be that similar reactions have been tried but found not to work. In the latter case, the unsuccessful result may not have been recorded in the literature.

For both these reasons, a strategy based simply on literature searching is unlikely to be competitive with the best synthetic chemists, who would, of course, use the literature to aid their synthetic designs. It may seem, then, that organic synthesis will remain a skill in which computers cannot compete with humans for some considerable time to come. However, this is not necessarily so.

Information technology enables computers to know the chemistry literature better than any person, but this, in itself, is not sufficient to design syntheses of new compounds. The use of information technology, coupled with methods for the computational analysis of novel reactions, may enable computers to design better syntheses.

The development of the World Wide Web has shown that it is possible for computers to communicate on a global scale, and this, coupled with developments in theoretical chemistry, may lead to computers making useful contributions to synthetic strategies in the near future. The Internet has been growing very rapidly, but it is unlikely to grow without limit. The Cambridge Chemistry Web server now handles about 50 000 requests for information each week and has been running for almost five years. After two years, the growth in use appeared to be approximately exponential, and so it was possible to estimate how the load on the server would increase. Based on just two years of data, the general shape of the following three years of growth was predicted with surprising precision, despite the constant addition of new material and new techniques. When the growth of the Internet levels off, the access to this server is also likely to level off. A recent report (Kaiser 1999) suggests that this may happen as early as 2003, with around 50 000 000 computers connected together. This suggests that accessible computer power is growing at many times the Moore's law prediction, but it is unlikely to continue to do so for very much longer. It will not give the thirty or so orders of magnitude that are required in order to solve organic synthesis by a brute-force approach.

The Internet allows the linking of computers that are tuned for database searching (and which may access a world-wide database of information, which is not limited by the published literature but also includes research results that are available only on the Internet) with computers that are capable of calculating chemical reactivity. It is now easy for me, for example, to do different sorts of literature searches on computers in Bath, Daresbury (Fletcher *et al*. 1996) and in Manchester, and to analyse the data using computers in Cambridge, all without leaving my office.

The next step would be to allow computers that can calculate chemical properties to interact automatically with computers that can search the chemical literature. This would enable the literature results to be extended to the precise systems of interest for a particular synthesis. If a new alcohol is being oxidized, then the effect of the surroundings could be calculated, while the experimental protocol could be taken from the paper. Thus, the literature results would guide the calculations. The calculations would also guide the literature searching, because the calculation may suggest a side reaction that could be checked in the literature. Literature precedent may be a more reliable guide than calculation as to which of several possible reactions is likely to work best.

It is only just becoming possible to use information technology to routinely search the chemical literature and to do chemical calculations that are directly useful to synthetic chemists. Each of these fields is likely to develop in a powerful way in its own right over the next decades. However, it is the interaction between these fields that gives the best chance of computers becoming the world's best synthetic chemists.

Chess is not solved, in the way the simple game noughts and crosses is solved, because the outcome of every game is not completely predictable. However, computers will usually win. In the same way, it may not be necessary for computers to analyse all possible routes to a molecule to be best at organic synthesis. It may be

enough simply to be successful at finding good routes. This makes the problem much easier, if it is assumed that there are many good routes. The computer would begin by guessing a route, and if that did not work, partly retracing steps, and trying again, thus reusing the information that had already been gathered or calculated so far as possible. Thoroughly exploiting the information that was developed with each potential synthesis would be a crucial step. The time required for conformation searching is dramatically reduced if similar molecules have already been investigated. For example, PM-toxin has a very complicated potential energy surface, which may be searched directly by traditional methods, or which may be mutated from the conformation search of an alkane, which is easier as it is particularly susceptible to a genetic-algorithm-based approach (Nair & Goodman 1998).

Will this allow syntheses to be automated? It depends how difficult syntheses are (and will provide a way of quantifying this). It may be that the best possible synthesis is not required, provided that a good route is available, as assessed by total cost (including waste disposal and safety precautions), by time required, by certainty of success, by ease of using robots to follow the procedure, and so on.

Organic synthesis is, and will remain, a very demanding discipline. Brute-force methods of calculating new synthetic routes will not be feasible for a very long time, and pure literature-based methods will also be very time consuming and will be restricted by the data available. A hybrid approach provides the best hope for designing a synthetic machine, and it is likely that such programs will become increasingly useful in the new millennium. Most of the elements of these programs are available now, but they are not sufficiently useful that they are an essential part of every chemist's work. An exhaustive solution may not be possible, so it is not certain that computers will beat people. However, the odds are stacked in favour of the computer, which will be able to develop and optimize many more routes than it is possible for synthetic chemists to consider directly. How difficult is organic synthesis? We will be taught the answer by the computers that extend the art beyond the heights reached by human scientists.

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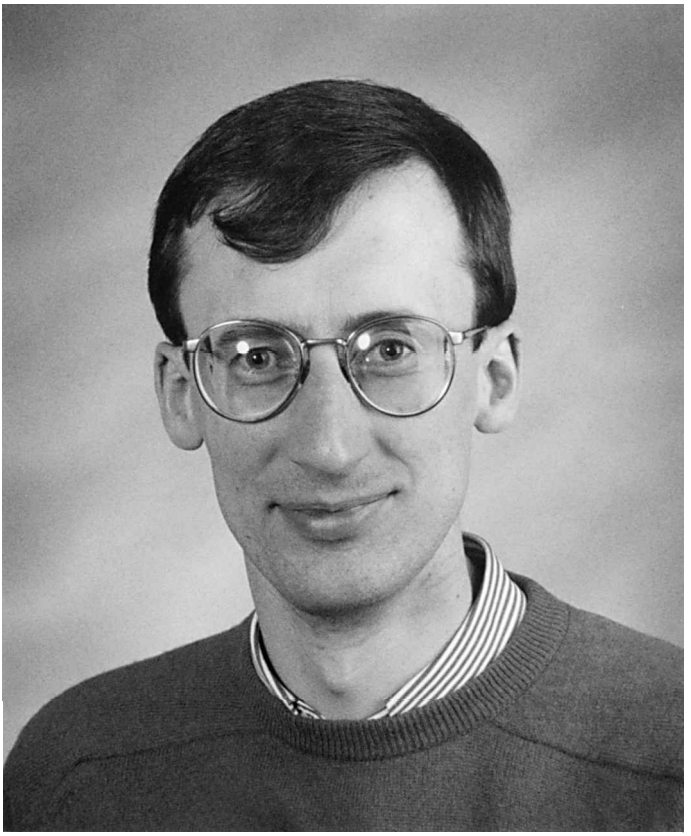
Jonathan Goodman studied chemistry at Cambridge, graduating with a BA in 1986, and with a PhD in organic chemistry in 1990. He then worked at Columbia University, New York, with Professor Clark Still, before returning to Cambridge as a Research Fellow at Clare College. He is now a Royal Society University Research Fellow in the Department of Chemistry, and uses both computational and experimental techniques to study organic chemistry. He is aged 35, and has recently published a book with the Royal Society of Chemistry, *Chemical applications of molecular modelling*, which introduces experimental organic chemists to computational techniques.



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