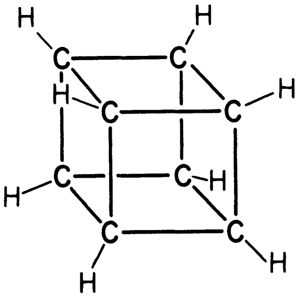
Marginalia

In Praise of Synthesis

Roald Hoffmann

Creation is wonderful. We admire Nature's work first—from simple things such as the hoarfrost that settled overnight on the brown shingles of the house, to that most intricate creation, repeated thousands of times each day, a human infant brought to term and born. Human creation second—Mozart and Lorenzo DaPonte, Elly Ameling and an English orchestra, 200 years apart, collaborating on a rendition of "Voi che sapete" that is so sweet and clear it almost hurts. Or David Hockney, assembling some 50 roughly developed prints into a photomontage in which the camera, Hockney, and we, like the eye, concentrate on a detail here, jump there, zoom in on a piece of the background.

And Phil Eaton and Thomas Cole, who synthesized a simple molecule, cubane, which has eight carbon atoms in the shape of a cube, each carbon also bearing a hydrogen:



It is the making of such molecules—chemical synthesis—that I want to praise. Synthesis is a remarkable activity that is at the heart of chemistry, that puts chemistry close to art, and yet has so much logic in it that people have tried to teach computers to design the strategy for making molecules.

Chemists make molecules. They do other things as well, to be sure—they study the properties of these molecules; they analyze, they form theories as to what makes molecules stable, why they have the shapes or colors that they do; they study mechanisms, trying to find out how molecules react. But at the heart of their science is the molecule that is made, either by a natural process or by a human being *(1)*.

The synthesis of molecules puts chemists very close to the arts and engineering. We *make* the objects that we study and appreciate *(2)*; in doing so we partake as much of the metaphor of creation as we do of discovery *(3)*.

There is not one way to make molecules; there are many ways. So let us look at some different kinds of chemical synthesis. The methods are shaped by scientific needs, economic considerations, tradition and aesthetics.

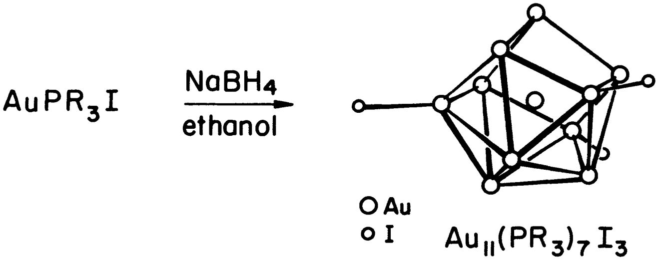
1. *Elemental synthesis*. You take substance *A*, perhaps an element, perhaps a compound, mix it with substance *B*, beat on it with heat or light, zap it with an electrical discharge. In a puff of foul smoke, a flash, an explosion, out pop lovely crystals of desired substance *C*. This is the comic-book stereotype of chemical synthesis. In general, an elemental synthesis is not considered by the chemical community to be a clever way of making molecules. Unless, unless—the product molecule has not been seen on earth before. This is how xenon tetrafluoride, XeF_4, was made *(4)*, with no pyrotechnics, but still by an elemental synthesis.

$$\mathrm{Xe} + 2\mathrm{F_2} \xrightarrow{\text{heat}} \mathrm{XeF_4}$$

Behind its creation was some clever reasoning by Neil Bartlett *(5)*, which allowed the makers of XeF_4 to imagine that the compound might exist. It was the first simple compound of a noble gas and a halogen. The uniqueness of creation can override stylistic reservations about how the product is made.

2. *Part by design, part by chance*. In that limbo between serendipity and logic, there stirs the vast majority of chemical syntheses. One has a rough idea of what one wants to do—cleave a bond there, form a new one here. One has read of similar reactions, on molecules that look vaguely like the one at hand, and so one tries (or more likely asks a graduate student to try) one of those reactions. It might work, it might not—perhaps the conditions must be juggled, the temperature changed, or perhaps one should follow a different regime of adding the reagents, giving them more or less time to mix. On the seventh run-through, something happens. There is mostly insoluble brown gunk in the reaction vessel, but if one separates the liquid, extracts it with another solvent, allows the material to crystallize, out come translucent lilac crystals of a product.

An example of such a synthesis is a reaction in which a spectacular gold cluster formed.



The chemists in Milan who did this work began with a simple gold phosphine iodide. They subjected it to reaction

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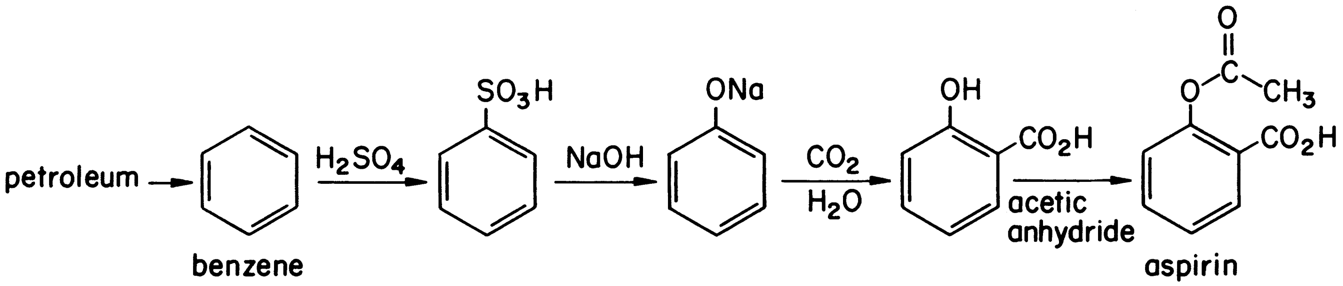

Figure 1. One industrial synthesis of aspirin from benzene.

conditions ($NaBH_4$, ethanol) that in some other cases had led to novel gold-gold bonding. The synthesizers had an idea that something interesting might happen. But I think it is fair to say they did not anticipate exactly what *did* happen, even though, and this is very important, they were well prepared to follow up and determine just what molecules were created in their flask. In fact, a marvelous cluster, one gold atom in the middle, with ten others (an icosahedron minus two) on the outside, assembled itself *(6)*.

3. *Industrial synthesis*. Figure 1 shows one of the ways in which aspirin is made commercially. The number of pills manufactured in the U.S. each year approaches the number of dollars in the nation's defense budget. From a petroleum fraction, benzene is separated out, then reacted sequentially with sulfuric acid, sodium hydroxide (lye), dry ice and water, and acetic anhydride (vinegar hiding) to yield acetylsalicylic acid, which is aspirin.

Some years ago, *Punch* published an apt verse commentary on synthesis and what are called "chemical feedstocks": *(7)*

> There's hardly a thing a man can name
> of beauty or use in life's small game,
> But you can extract in alembro or jar,
> From the physical basis of black coal tar:
> Oil and ointment, and wax and wine,
> And the lovely colours called aniline:
> You can make anything, from salve to a star
> (If only you know how), from black coal tar.

The making of aspirin, like most fine chemical manufacture, begins from a portion of refined petroleum. Right there is a problem, and a challenge—how to make those complex structures from sources less easily depleted.

An important factor in any industrial synthesis is safety. The manufacturing process must not injure the health of the workers, and the final product must be safe for the consumer. In this context, people have speculated whether aspirin would be allowed on the market as a nonprescription medication if it were newly introduced today.

The overriding imperative in industrial synthesis is cost. Starting products and reagents had better be as close as possible to earth, air, fire and water (and fire is getting awfully expensive). All of the reagents in the aspirin synthesis are on the "top 50" list of the chemical production hits chart, being among the highest in volume of production and among the lowest in cost. Expense also drives producers to optimize the efficiency of synthesis. If a step in a synthesis gives a yield of 90 percent (that is, 90 percent of the theoretically possible amount—more on yields below), then an improvement to 95 percent, perhaps through a new catalyst, might provide a competitive advantage of millions of dollars. In the past, this led to research strategies such as "take the next chemical off the shelf and try it." Today the progressive segment of industry invests in basic studies of the mechanisms of their reactions, the rational way to improve a process.

The competitive pressure to reduce cost is also the source of much creativity in industrial synthesis. The academic chemist can and will flit to the next exciting problem if one synthesis doesn't work out. The industrial chemist does not have that choice. So he or she pushes on, often to ingenious solutions *(8)*.

4. *Planned synthesis*. Actually, it is in the academic setting that many of the masterpieces of synthesis are created. The constraints of cost are relaxed, though they are still there. Imagination is set free. Marvelous syntheses result. Here is one, already mentioned, that of cubane. This carbon die is an unnatural product; it was made not because it was thought useful *(9)*, but because it is beautiful, in a simple Platonic-solid sense. It was also made because it was there, like the proverbial mountain, waiting to be made. Others failed to synthesize it before two people at the University of Chicago succeeded in 1964.

Figure 2 is a diagram redrawn from the original paper by Eaton and Cole, showing how they did it *(10)*. We have before us ten molecules, with nine arrows, representing reactions, between them. Above each arrow is the briefest mnemonic description of the reaction conditions. Each reaction might be composed of from five to twenty distinct physical manipulations: weighing out reagents, dissolving them in a solvent, mixing, stirring and heating, filtration, desiccation, and so on. A step might take an hour or a week. And the scheme does not include the laborious and ingenious analytical chemistry required to identify those intermediate molecules.

At the end of the synthesis is cubane. The chemist's sign for it is just a simple polyhedron; the professional privy to the code knows that each vertex stands for CH. At the beginning of the synthesis is molecule I. It doesn't look simple—one thinks that at the start of any construction there should be readily available materials. Actually, starting material I *is* easy to make. The Chicago chemists had synthesized it earlier, in three steps, from another molecule that costs pennies per gram.

Below each arrow is a percentage. This is the yield, the percent of the theoretically possible product that is actually obtained. Our synthesizers got 85 percent of that theoretical yield for the first reaction in the synthesis. In subsequent reactions, they got yields ranging from 30 percent to 98 percent. You might think that the main reason they wrote down these yields is to demonstrate efficiency. Indeed, it is easy to calculate how many carloads of the starting material they would have to use to get one milligram of cubane, if each

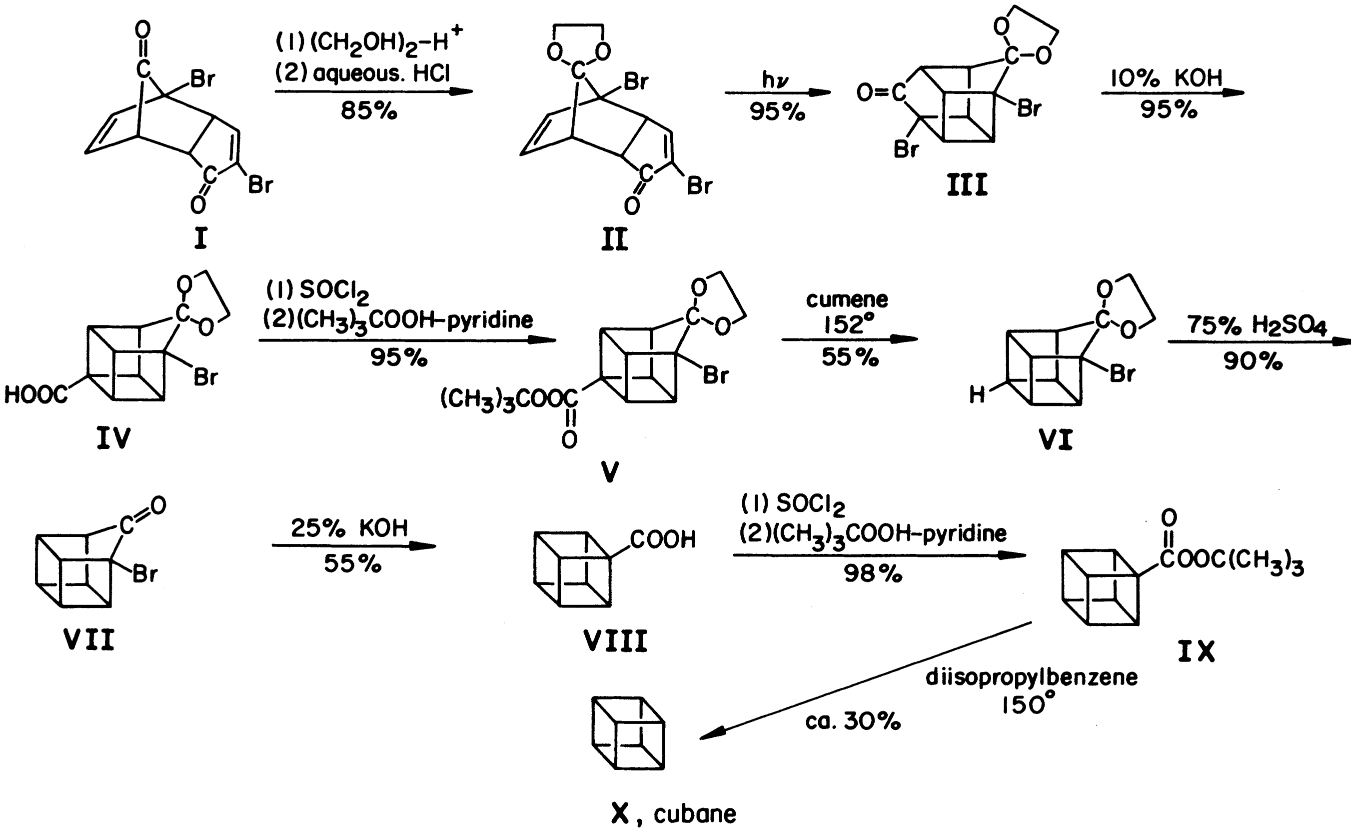

Figure 2. Synthesis of cubane, as originally performed by Philip Eaton and Thomas Cole.

step were 10 percent efficient. But that is not the main reason these workers listed the percent yield.

The yield in a chemical reaction is an aesthetic criterion. To appreciate this, think about how one might get only a 10 percent yield. A reaction is a sequence of physical manipulations performed by a fallible human being using imperfect tools. One way to get a 10 percent yield is to spill 90 percent of the solution in the course of a transfer from a flask to a filter funnel. Sloppiness will not impress people, in science or in art.

Suppose every transfer is meticulously done. The craftsmanship is high. Still one gets a 10 percent yield. Now it is not human hands that are at fault, it is the mind. Nature has paid no attention to our design, but has decided to do something else with 90 percent of our material. That does not show control of mind over matter, and it does not draw admiration. Maybe there's a better way to carry out that reaction step. A sequence of high-yield reactions, such as the sequence in the cubane synthesis, defines elegance in chemistry.

There is high logic in synthetic strategy. The design of a multistep synthesis resembles the making of a chess problem. At the end is cubane—the mating situation. In between are moves, with rules for making them. The rules are much more interesting and free than those of chess. The synthetic chemist's problem is to design a situation on the chessboard, 10 moves back, which has the most ordinary appearance. But from that position, one player (or a team of chemists), by a clever sequence of moves, reaches the mating position no matter what the recalcitrant opponent—the most formidable opponent of all, Nature—does.

The obvious logical content of synthesis has inspired people to write computer programs to emulate the mind of a synthetic chemist. The design of such programs is a high challenge to workers in "artificial intelligence" and "expert systems," as well as to chemists. The programming is an educational act of great value; chemists who have worked on these programs have learned much about their own science as they analyzed their own thought processes. Use of these programs is now common in some industrial laboratories; they can be of help in routine syntheses.

Can the synthesis programs suggest *interesting* syntheses, the kind that if turned to practice could be published in a good chemical journal? I think this remains an open question. The papers of workers in computer-assisted synthesis typically illustrate the capability of their programs by demonstrating that the programs suggest routes to difficult targets identical to paths conceived earlier by other good (noncomputerized) chemists. But I'm still waiting for the paper that begins: "There is great interest in a new antiviral agent, Bussacomycin-F17, isolated from the slime mold *Castela manuelensis*. We attempted a total synthesis of this molecule with 15 asymmetric centers, but were unsuccessful. We then turned to the program MAGNASYN-3, which suggested the eventually successful synthesis shown in Figure 1...."

The psychology of human beings leaves us ill-prepared to admit that we could be replaced by a computer program, although we may be ready to concede that other people can be.

A chemical synthesis is obviously a building process. One therefore sees architectonic considerations, and the aesthetics of architecture figure prominently. Note, for instance, that intermediates in the synthesis of cubane are more complicated than the starting material or product. Why is this so? Well, scaffolding has to be built to hold pieces of the structure in place while other parts are assembled. A specific detail gives some further insight. In substance I there are two ketone groups, or CO groups bonded to two other carbon atoms. The reaction from I to II transforms one of the ketone groups into a five-membered ring but leaves the other group alone. Then Cole and Eaton get to work on that other ketone, changing it from CO to COOH (III→IV), the COOH to $(CH_3)_3COOCO$ (IV→V), and that to H (V→VI). In VI→VII, they uncover the second ketone group and then proceed to do to it the same violence they did to the first one (VII→VIII→IX→X). What a waste of effort! Why not do both groups at once?

What you see here is the basic and simple idea of a "protecting group," the padding or concealment of one piece of a molecule while a transformation is done on another piece. Then the protecting group is removed. When cubane was first being made, Eaton and Cole were fearful that this molecular skeleton might be unstable. So they proceeded in small, cautious steps, using this strategy of protection.

They need not have worried. We know today that both ketone groups can be converted to COOH in one step *(11)*. That this was not attempted the first time the molecule was made in no way detracts from the synthetic achievement. It points out the "historicity" of this human activity, as of all others: something was done, perhaps not as well as it could be done today, in tentative steps, but still created, for the first time, by human intelligence, human hands.

Synthesis is a building process, but what a marvelous "hands-off" kind of building! This is not the nailing together of a wood box shaped like a cube, or even a Palladian villa. In the reaction flask there is not one molecule, but 10^{23}. They are tiny. They are all bouncing around, chaotically doing their own thing. And yet on the average they are being made to do what *we* want them to do, driven only by the external macroscopic conditions we impose on the flask and the strong dictates of thermodynamics. We create local order, to order, through an increase of disorder in the surroundings.

Chemical synthesis not only shares some of the aesthetic criteria of art; I think it *is* art. At the same time, it is logic. To quote a modern master of synthesis, E. J. Corey:

"The synthetic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine, and even to create. These added elements provide the touch of artistry which can hardly be included in a cataloguing of the basic principles of Synthesis, but they are very real and extremely important....

"The proposition can be advanced that many of the most distinguished synthetic studies have entailed a balance between two different research philosophies, one embodying the ideal of a deductive analysis based on known methodology and current theory, and the other emphasizing innovation and even speculation. The appeal of a problem in synthesis and its attractiveness can be expected to reach a level out of all proportion to practical considerations whenever it presents a clear challenge to the creativity, originality and imagination of the expert in synthesis." *(12)*

References

1. For a discussion of the natural/unnatural dichotomy see R. Hoffmann, 1990, *New England Review and Bread Loaf Quarterly* XII (No. 4):323.
2. This thought was expressed by Marcellin Berthelot, 1860, *Chimie Organique Fondée sur la Synthèse*, Tome 2, Paris: Mallet-Bachelier. I am grateful to Jean-Marie Lehn for this reference. The special role of chemistry, its contrast to parts of physics and resemblance to art and engineering, is taken up in an article by J.-P. Malrieu, 1987, *L'Actualité Chimique* No. 3, p. ix. He coins the apt descriptor of technopoïese to characterize chemistry.
3. See R. Hoffmann, 1990, *American Scientist* 78:14.
4. H. H. Claassen, H. Selig, H. G. Malm, 1964, *Journal of the American Chemical Society* 84:3593.
5. N. D. Bartlett, 1962, *Proceedings of the Chemistry Society*: 218.
6. L. Malatesta, L. Naldini, G. Simonetta and F. Cariati, 1966, *Coordination Chemistry Reviews* 1:255; V. G. Albano, P. L. Bellon, M. Manassero and M. Sansoni, 1970, *Chemical Communications* 1210; F. Cariati and L. Naldini, 1971, *Inorganic Chimica Acta* 5:172. The crucial crystal structure that revealed the Au_{11} cluster was for an SCN derivative: M. McPartlin, R. Mason and L. Malatesta, 1969, *Chemical Communications* 334.
7. Quoted by J. Read, 1958, in *Perkin Centenary London; 100 Years of Synthetic Dyestuffs*, London: Pergammon Press, p. 23.
8. For some astute observations on the contrast of creative chemistry in industry and the universities see G. S. Hammond, 1987, *Chemtech*: 140.
9. There is now, 25 years after its synthesis, some interest in derivatives of cubane as pharmaceuticals, explosives and fuels. Pilot-plant production, in kilogram quantities, is proceeding.
10. P. E. Eaton and T. W. Cole, Jr., 1964, *Journal of the American Chemical Society* 86:3157.
11. P. E. Eaton, private communication.
12. E. J. Corey, 1967, *Pure and Applied Chemistry* 14:30.
13. This essay was published in a slightly different form in *Negative Capability* (1990) X (No. 2, 3):162.