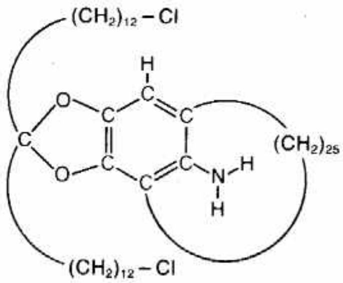
Marginalia

Molecular Beauty II: Frogs about to Be Kissed

Roald Hoffmann

In the first essay under this rubric I looked at a molecule of some complexity and saw in its structure that it was lovely (*1*). Can one say the same about structure 1? Not at first sight. What are those dangling $(CH_2)_{12}$–Cl chains at left? Or the unsymmetrical $(CH_2)_{25}$ loop at right, or the NH_2? The molecule is, if not ugly (there are no ugly molecules, says this most prejudiced chemist), at least plain. It's not an



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essential component of life, it's not produced in gigakilogram lots. In fact, its purpose in life is not clear.

The last sentence contains a clue to what makes this molecule, a frog that is a prince, beautiful. Chemistry is molecules, and it is chemical change, the transformations of molecules. Beauty or elegance may reside, static, in the very structure, as we saw for the molecule $NaNb_3O_6$ (*1*). Or it may be found in the process of moving from where one was to where one wants to be. History and intent have enormous transforming power; the molecule depicted in structure 1 is beautiful because it is a waypoint. Or, as they say in the trade, an intermediate.

Where is one going? To a catenane (structure 2), two interlocking rings of carbon atoms, not chemically combined but held together like the links of a chain. Why should people try to make a catenane? For no particular reason. For the best reason, because none was made before. How to make it? Here's one strategy, which I will


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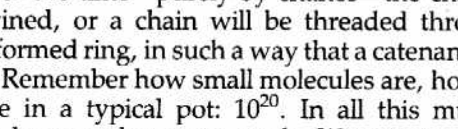

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term a statistical one. A typical chemical reaction is a cyclization, schematically written out in structure 3. If we run the cyclization of a long chain of molecules, some fraction of the time—purely by chance—the chains will be entwined, or a chain will be threaded through an already formed ring, in such a way that a catenane will be formed. Remember how small molecules are, how many there are in a typical pot: 10^{20}. In all this multitude, statistics have a chance to work. Wasserman actually realized this in 1960, when synthesizing a catenane for the first time (*2*).

The statistical procedure works, albeit inefficiently. There are other ways to craft the catenane topology. One beautifully conceived synthesis is due to Schill and Lüttringhaus (*3*). Their logical scheme is

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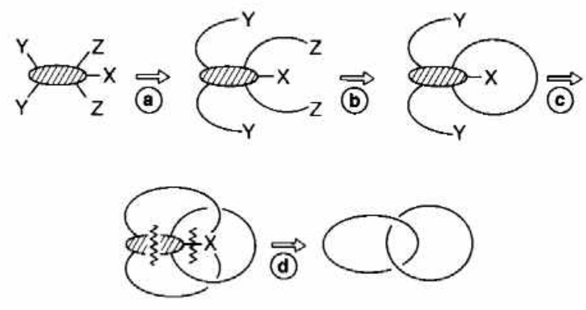

summarized in structure 4. The starting point is a molecule with lots of specifically disported functionality. In chemistry, a functional group is a set of bonded atoms whose properties are more or less invariant from one molecule to another. The most important of these properties is chemical reactivity, the "function" of the group. To put it another way, in the context of doing chemistry on a molecule, functional groups are the *handles* on a molecule. The transformation of functional groups, and particularly the predictability of their reactions, are a crucial element in the conceptual design of syntheses in organic chemistry. Common functional groups might be R–OH (alcohols), R–COOH (organic acids), R–COH (aldehydes), R–X (X = F, Cl, Br, I, or the halides), where R is anything. The substituents X, Y, and Z in structure 4 are functional groups.

Step a in 4 elaborates the Y and Z functional group handles into long chains. Step b is a closing up, or cyclization, of one set of chains. Step c is a different kind of cyclization, another linking up, now of the other set of chains to the remaining core functionality X. Step d, perhaps several steps, is a fragmentation: the core from which the reaction was initiated, on which all was built, is now mercilessly torn apart, revealing the catenane.

Several points about this process are important: (i) the synthesis is architecture, a process of building, and (ii) as such it requires work. It's easy to write down the logical sequence of steps, as I have. But each step may be several chemical reactions, and each reaction a more or less elaborate set of physical processes. These take time and money. (iii) The architectonic nature of the process almost dictates that the middle of the construction have molecules that are more complex than those at the beginning and the end (*4*). Note (iv) the essential topological context of chemistry. It's evident not only in the curious topology of the goal, a catenane, but in the very process of linkage that pervades this magnificent way of building.

To return to the reality of the specific, the moment scheme 4 is laid out it is clear what structure 1 is. It's the

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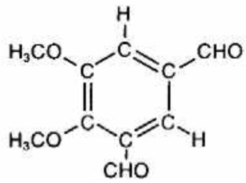
crucial point in the middle, after step b and before step c. It's poised to cyclize, the chlorines at the end of the $(CH_2)_{12}$ chains set to react with the NH_2 group. The synthesis by Schill and Lüttringhaus begins with mole-



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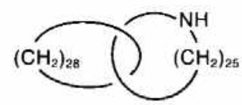

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cule 5 and ends with catenane 6, in which a ring of 28 carbons interlocks with another ring with 25 carbons and one nitrogen.

But while getting to structure 6 is sweet, it should be clear that what is important is "getting to," the process. That process is reasonably linear (although 4 makes us think it's more linear than it is). One might suppose that any step in a linear chain of transformations (a — b — c — d — e) could claim primacy of significance. Indeed, the steps in a synthesis may differ vastly in their difficulty, and therefore in the ingenuity invested to accomplish them. The unpublished lore of chemistry abounds with tales of a fantastically conceived, elegant synthesis in which the very last step, thought to be trivial, fails.

Nevertheless, I will advocate a special claim for a molecule somewhere in the middle of the scheme, the molecule most complicated relative to the starting materials and the goal; the molecule most disguised, yet the one bearing in it, obvious to its conceiver but to few others, the surprise, the essence of what is to come (5). It's the col of complexity, and the only way from this beautiful molecule is on, on.

References

1. R. Hoffmann. 1988. *Am. Sci.* 76:389.
2. E. Wasserman. 1960. *J. Am. Chem. Soc.* 82:4433. For an elegant Möbius-strip approach to catenanes see R. Wolovsky, 1970, *J. Am. Chem. Soc.* 92:2132; D. A. Ben-Efraim, C. Batich, and E. Wasserman, 1970, *J. Am. Chem. Soc.* 92:2133. See also the ingenious synthesis of J.-P. Sauvage and J. Weiss, 1985, *J. Am. Chem. Soc.* 107:6108.
3. G. Schill and A. Lüttringhaus, 1964, *Angew. Chem.* 76:567; 1964, *Angew. Chem. Intl. Ed.* 3:546.

   A. Lüttringhaus and G. Isele, 1967, *Angew. Chem.* 79:945; 1967, *Angew. Chem. Intl. Ed.* 6:956.

   G. Schill, E. Logemann, and W. Vetter, 1972, *Angew. Chem.* 84:1144; 1972, *Angew. Chem. Intl. Ed.* 11:1089.
4. For some leading references on complexity in chemical synthesis, chemical similarity, and chemical "distance," see S. H. Bertz, 1982, *J. Am. Chem. Soc.* 104:5801; M. Wochner, J. Brandt, A. von Scholley, and I. Ugi, 1988, *Chimia*, 42:217; J. B. Hendrickson, 1977, *J. Am. Chem. Soc.* 99:5439.
5. For an inspiring, original presentation of the achievements of organic synthesis see N. Anand, J. S. Bindra, and S. Ranganathan, 1988, *Art in Organic Synthesis*, 2nd ed., Wiley.