

Learning from Molecules in Distress**

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extreme conditions · gedanken experiments ·
psychology of research · strained molecules

From the time we first got an inkling of the geometries and metrics of molecules, the literature of organic chemistry has contained characterizations of molecules as unstable, strained, distorted, sterically hindered, bent, and battered.^[1] Such molecules are hardly seen as dull; on the contrary, they are perceived as worthwhile synthetic goals, and their synthesis, or evidence of their fleeting existence, has been acclaimed.

What is going on here? Why this obsession with abnormal molecules? Is this molecular science sadistic at its core?

Let's approach these questions, first describing what is normal for molecules, so we can define the deviance chemists perceive. After a digression into the anthropomorphic language chemists generally use and the psychology of creation in science, we will turn to the underlying, more serious concern: "What is the value of contemplating (or creating) deviance within science?"

The Denumerable, Flexible Chemical Universe

As many as 366319 different eicosanes ($C_{20}H_{42}$) are conceivable, not counting optical isomers. And an enumeration of the components of a reasonably constrained universe of all compounds with up to 11 C, N, O, and F atoms comes to >26 million compounds.^[2] An important feature of the chemical universe is that the tree of possible structures is denumerable. At the same time, the playground of chemical structures is subject to systematic elaboration, through the decoration of an underlying skeleton by functional groups of some stability. Very quickly a multitude turns into a universe—of structure and of function.

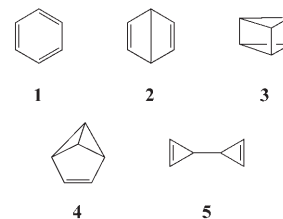
Thinking of these molecules as fixed, rigid structures is natural—don't they look like olive-and-toothpick assemblages, prettied up by computer rendering? And one can certainly get a long way in organic chemistry in the classical, mechanical mode. But the atoms in a molecule move continually, deviating, oscillating, as if held by springs, around an average position. The hexagonal structure of the benzene ring (a molecular tile, seemingly ever so flat and rigid as the one on your bathroom floor) has become an icon of chemistry just as the angled water molecule. Yet that tile is not rigid; it moves—and one can see the deformations/deviations by looking at its vibrational (what a telling name!) spectrum.

Recognizing the Abnormal

Chemistry is more than graph theory; it is graph theory with a metric (bond lengths, bond angles). From the time structural theory was established, and

progressing into the 20th century, normal behavior—tetrahedral four-coordinate carbon atoms, the coplanarity of the six atoms in ethylene, the planar benzene hexagon—was established. Bonding theories consonant with that normality—Lewis structures, valence bond pictures—gained currency. And measures of the cost of departing from the norm were obtained, both experimentally (force constants for those vibrations) and later, as calculations became reliable, theoretically. From that knowledge, mainly coming into our hands in the second half of the 20th century, derives our perception of the "normal" molecule, and, by contrast, an intuition for what is unusual.

The isomers of benzene (**1**) are a case in point. Of the $(CH)_6$ graphs, Dewar benzene (**2**),^[3] prismane (**3**),^[4] benzvalene (**4**),^[5] and bicyclopropenyl (**5**)^[6] were perceived as "makeable," or "not too unstable" (Scheme 1). And, in remarkable synthetic achievements, they were made. Other isomers were also recognized, no assistance needed from computations, as just plain impossible, as **6**, a "realization" of the Claus formula of benzene.^[7] And still other $(CH)_6$ isomers, such as the biscarbene **7** (or any molecule derived by breaking a single or double bond in the benzene isomers **1–5**) are admitted by chemists as possible metastable species (Scheme 2).^[8]

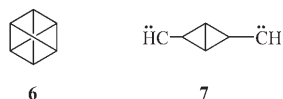


Scheme 1. The isolable $(CH)_6$ isomers.

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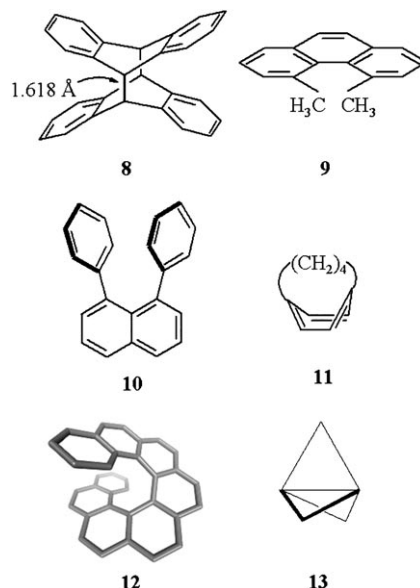


Scheme 2. An “impossible” and a highly reactive (CH)₆ isomer.

The impediments to stability can be quantified energetically. A preliminary note is in order here: in chemistry, especially organic chemistry, real stability is relatively unimportant, and metastability (kinetic persistence) more than suffices. To put it one way, every organic molecule in our bodies is thermodynamically unstable in the presence of oxygen, every one can (and will eventually!) be oxidized to water and carbon dioxide. But we burn only figuratively, with passion. The barriers to many exothermic chemical reactions are high—you can read this paper without fear that it will start burning in your hands. And this ensures the persistence of molecules under ambient terrestrial conditions for the time a slow chemist (or life itself) requires.

Focusing on thermodynamics, one could compare, for instance, the energetics of hydrogenation of cyclopropane and cyclohexane and find the former is more exothermic by 27 kcal mol⁻¹.^[9] Or we can estimate departures from the normal by other measures: One can look at the elongation of the linking single bonds in the anthracene photodimer **8**,^[10] or the drift of electrons away from the methyl groups of 4,5-dimethylphenanthrene (**9**),^[11] gauged by the NMR chemical shifts, the bending away from each other of the phenyl groups of 1,8-diphenylnaphthalene (**10**),^[12] the boatlike deformation of the benzene ring of [4]paracyclophane (**11**).^[13] Or the eponymic structural essence of a helicene (**12**, [8]helicene,^[14] Scheme 3) and the [1.1.1]propellane (**13**), in which the four C–C bonds of the tetrahedral carbon atom are folded into one hemisphere; it “looks” prohibitively strained, yet is a stable compound.^[15]

The reader will have noticed that in our sampling of stressed molecules we have focused primarily on hydrocarbons. We could have chosen problematic heterocycles or reactive molecules such as vinyl alcohol. Without heteroatom reactivity there would be no life, nor would many (if any) of the exemplary



Scheme 3. A (small) selection of distorted hydrocarbons.

hydrocarbons we cite have been made. Chemical reactivity is set by the differences in functional groups. And the vast majority of these contain N, O, and S atoms, and in their interactions and peculiarities set as many obstacles to persistence as the hydrocarbons we cite. But we’d like to start somewhere in a journey through “unhappy” molecules, and the archetypal hydrocarbons are a good place.

So some molecules emerge as bent and battered. But why should they be of interest, and why turn to such descriptors in their characterization? Is it telling us something about the molecules, or about us? Let’s talk first about the language.

Anthropomorphisms (and Metaphors) Are OK

The colloquial and anthropomorphic nature of the descriptors used for the molecules of interest—strained, hindered, battered, unstable—are revealing. And we suspect that such language makes some of our colleagues uncomfortable. It shouldn’t. Scientists think words don’t matter, that equations, formulas, spectra do. But the facts are mute; without words no sense could be made of this world. And, as Wittgenstein said: “*Die Grenzen meiner Sprache*

bedeuten die Grenzen meiner Welt.”^{[16][*]} Words, first of all, are friends; they humanize the inanimate world, form a liaison, a bond with a human being. Words mislead much less than they encourage, for it is just through their anthropomorphism that they provide a rationale for the often tedious labor of chemistry.

Words—rather than physical formulae—are also very well suited to describe the dynamic aspects of chemistry: contrast “backside attack” vs. “calculated trajectory.” Or consider the phrase “an eclipsed conformation”—what a clear and convincing description of a certain steric situation! The metaphor is astronomical; were we to give the Cartesian coordinates of the respective atoms in that eclipsed conformation, it would be “more precise” but perhaps tell us even less, especially since the exact location of atoms is often not needed in chemical reasoning.

If you haven’t thought through the science underneath plain language, words can cause confusion. But if you understand, then colloquial, anthropomorphic, colorful expressions make inanimate matter spring to life.

Reasons for Making Molecules in Distress

Let us return to our chemical universe, replete with stable and metastable molecules. From the 19th century on, the synthesis of molecules that deviated from the norm took a special place in the imagination of chemists. There are many examples to point to, molecules that violate Bredt’s rule^[17] or the classical double-bond rule, or organometallic complexes in which the CO ligand bonds to a transition metal through its oxygen atom. Once theoreticians could contribute more or less reliably, they took to this game with a vengeance—one of the authors’ strategy for stabilizing square-planar carbon is a good example: a veritable menagerie of (largely) hypothetical molecules was generated.^[18]

But why do this? In the first instance the reasons are psychological. The molecules are there, they are perceived as

[*] “*The limits of my language mean the limits of my world.*”

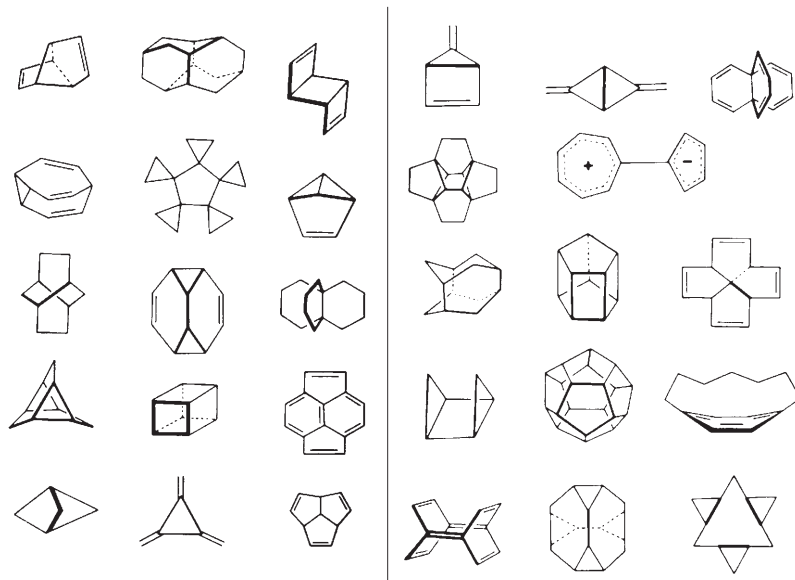
intriguing to weird, so people want to make them. So it makes sense to inquire how the psyche enters into creation.

Psychological Reasons

Psychology does not find a comfortable place in the ritualized, ossified format of a typical scientific article. But, as one of us has repeatedly argued,^[19] the subconscious forces in our psyche are the motive force. And if they aren't entirely savory, they are part of the beauty of human creation. Do we have to list all the ways angelic science and art has been and is made by men and women who are far from angels? This is not an excuse for being unethical—creation demands that we consider its consequences—it is just an awareness of the reality of making the new in art and science.

One reason for synthesizing some pretty unhappy molecules is simply the desire to do what has not been done before. And to be praised for it. Ideas and actions are our stock in trade—a curious thing in a way, since science is after universals. If $E=mc^2$ is true and benzvalene persists in air, does it matter in the long run who came up with the equation or made the molecule? Oh, it does. Scientists are driven as much by emotions as by reason—otherwise whence the overpowering wish to be the first? To be quoted? To be the most often quoted? Science is done by scientists—not machines—and scientists, as human beings, crave recognition^[20] for their ideas and the fruit of their handiwork.

All of us of a certain age remember the inner front and back covers of the Cram and Hammond textbook of organic chemistry, with its drawings of molecules made and not made at the time of writing (Scheme 4).^[21] And Hilbert's theorems have played a similar, long-lasting role in mathematics, as challenges.^[22] It is in the nature of human beings to try to do what has not yet been done. One of the authors (R.H.) resisted R. B. Woodward putting in the original paper on orbital symmetry, referring to exceptions, the statement "There are none!"^[23] R.H. was wrong; the phrase was a creative provocation.



Scheme 4. Cram's and Hammond's challenge to hydrocarbon chemists.

Another motive force, always at work in scientists, is curiosity, with no thought of reward, no reaching after putative praise. Are there space-filling networks of carbon other than graphite, in which every atom is trigonal (three bonds going off at 120°)?^[24] If CO and N₂ are common or known ligands in organometallic compounds, why not BF?^[25] Can one make C–C bonds that are really short?^[26]

It's just so much fun to explore that chemical playground, asking "What if?" or "Why not?" questions. One can feel guilty; for the time spent in following one's curiosity does not deal with that other aim of science—melioration of the human condition. Through technology we can change and have changed the world, for the better, by and large. But more needs to be done for humanity; why play games?

There are games and there are games. We are *homo ludens*;^[27] to outlaw games would probably banish creation altogether. Games pleasure people, and games advance chemistry. Time and time again, we see a use materializing in molecules made for no great purpose. Consider also that the world of useful natural products did not evolve for medicinal chemists.

The reason for playing these experimental and theoretical games is more than curiosity. We probe the limits, so as to learn. As Jerry Berson says, "*Some-*

thing drives us to go deeper and push the limits. That is the expectation—or at least the hope—that something new will emerge when we explore those far regions."^[28] Elsewhere Berson has described aptly the mix of psychological factors motivating synthesis of unnatural molecules: "*As chemists find themselves stirred by the mysterious allure of the symmetrical and the beautiful, aesthetic and self-challenging motivations also become apparent in many such instances. Like the impulse driving the heroic geographical expeditions, the urge to explore is often mixed with a sheer will to surmount risk or hazard in order to triumph over adversity. The parallel that comes to mind is George Mallory's famous answer when he was asked why he wanted to climb Mt. Everest: 'Because it is there.'*"^[29]

The recognition of psychological factors—of reaching for praise and priority, of curiosity of how things work and why, of exploration in the search for understanding, of game-playing, is important. For when we couple these motive forces with the natural anthropomorphism that enters our language and thought as we deal with molecules—they are "strained," they do or do not "want to" react in these ways—we enter into a psychological relationship with an inanimate object. And this is perfectly OK.

In the course of doing normal (good!) science, curiosity, a desire to understand, become mixed up with forces in our psyche that power creation. Of course the hagiographic ideology of science tries to nudge those forces out of the picture in its creation of an (artificial) Apollonian universe. The strategy for doing so in any activity as imaginative, as so inherently human, as passionate as science, can only be suppression. A more balanced view of the creative work of science would find a place for the streams Nietzsche called Apollonian and Dionysian.^[30]

Molecular Sadism?

Louis-Donatien-Alphonse-François, the Marquis de Sade, is a striking and contentious figure straddling the 18th and 19th centuries. His name labels forever a despicable human trait, of taking satisfaction if not delight in inflicting physical suffering on others.

The characterization of what chemists do to strained molecules as molecular sadism is no more than what the expression aims to be—a cute turn of phrase. As a description it is facile if not puerile, and does not stand up under consideration. Yet attempts at being funny often do betray underlying tensions. The relationship of human beings and the objects of their creation or contemplation (here compounds/molecules) is never simple. Into it enter our irrepressible tendency to anthropomorphize and the satisfactions and travails of the creation. While we don't think sadism comes into the equation, it is nevertheless interesting to look at Sade, his writings, and their interpretation, and see if there is something other than mental illness in them.

The eventful story of the Marquis de Sade has been told several times;^[31,32] yet the interpretation of his life and writing remains controversial.^[33–36] Born in an aristocratic family, Sade grew up to be a libertine. In an age where the privileged could escape the consequences of their actions if their victims were of a lower class, his were excessive. And he had a persistent and vengeful mother-in-law, Mme. de Montreuil. A series of imprisonments ensued. In the last of these, in the Bastille and at Charenton,

he began to write. Sade's accommodations to the revolution ran afoul first of Jacobin, then of Napoleonic mores. All in all, the Marquis spent some 30 of his 74 years confined.

The characteristic features of Sade's philosophy, obsessively shaped by his personality, include: an opposition to all authority, atheism, sexual freedom (including an unusual recognition, for its time, of female sexuality), and extreme libertarianism. And, in his actions, and in his imaginative fictions, a penchant for a mix of cruelty and sex. This celebration (perhaps that's not the right word, for much of the repeated fornication in Sade's writings is joyless) of inflicted pain has rightly earned the Marquis the ill fame of sadism with a lowercase s.^[37]

Strangely enough, one can even find in Sade's writings passages that seem close to science. But then we read on, and this Heraclitean bent, so close in spirit to the eternal change that underlies chemistry, is put in the service of... rationalizing murder: "*Et voilà donc ce que c'est que le meurtre: un peu de matière désorganisée, quelques changements dans les combinaisons, quelques molécules rompues et replongées dans le creuset de la nature, qui les rendra dans quelques jours sous une autre forme à la terre; et où donc est le mal à cela? Si j'ôte la vie à l'un, je la donne à l'autre: où est donc l'offense que je lui fais?*"^{[38][*]}

This is Juliette speaking, yes. But it is also Sade. Moreover, this passage is not an exception, but a piece of a repetitive litany of perversity. There is no way that any rational or ethical human being can follow Sade here.

Let Sade, sick as he was, rest. The synthesis of real molecules, even ones that are not "normal," has precious little to do with sadism. The ethical considerations that should accompany bring-

ing a new compound into the world preclude that.

Still, there are things in Sade's philosophy that have intrigued 20th century writers from Roland Barthes to Simone de Beauvoir. For the Marquis, that destroyer of normalcy, was the border violator par excellence. He was an intellectual libertine, as much as he was a sexual one—one who believed that everything was possible for the human spirit. And that the human condition was in fact one of ringing all the changes on creation.

There is another connection of science and Sade. Pierre Laszlo has remarked that "*...the monstrous is a major theme of Sade. And the Promethean push by scientists for the limits of their science, whatever field they are engaged in, and notwithstanding Mary Shelley, draws from the Early Modern mentality. Western science is underlined by its sense of wonder. Monsters are and remain an integral part of it. Wondering at monsters marks early science and carries into modern science. Such seeking for the abnormal is blatant in chemistry, in the exploration of unusual natural products and in the drive to make stressed molecules.*"^[39]

In no way descending with Sade into perversity, we think that this makes it less than absurd to contemplate the ideas of the poor Marquis (not sadism) in the context of chemistry.

A Better Metaphor

The purpose of studying unhappy molecules is *not* delight in their squirming under stress. We learn, or try to learn, from the abnormal. Actually, if you want a metaphor, bringing succour might serve as well as torture. The moment one of us looked, really looked, at that poor square-planar carbon atom, he and his co-authors were thinking of a strategy to stabilize it, to give it a chance, just a chance, for existence.

So, Will Any Molecule that Can Be Imagined Be Made?

The understanding we have of molecules is partial and incomplete in every aspect, as many examples from the

[*] "So this is what murder is! A little organized matter disorganized; a few compositional changes, the combination of some molecules disturbed and broken, those molecules tossed into the crucible of Nature, who, re-employing the selfsame materials, will cast them into something else so that in a but a day or so they shall reappear in the world again, only guised a little differently; this is what they call murder—truly now, in all seriousness, I ask myself, where is the wrong in murder?"

history of chemistry show. Future generations of chemists will look at our DFT-calculated electron distributions in molecules in the same way we look at Kekulé's "sausage structures". And often a theory describes something fortuitously; probing it at the extremes helps one see its limitations.

Repeatedly, the making of molecules that are untypical or abnormal tests our understanding of that fundamental yet fuzzy entity—the chemical bond.^[40] And it stretches the limits of the efficiency of our laboratory techniques. An unprotected silicon–silicon double bond, an ethylene substituted by donors and acceptors in a push–pull pattern, these are all wonderful probes of our understanding, of the factors that make normal chemistry such a productive enterprise.

With time, a simple way was devised to account for bonding in molecules, providing reasonable guidelines for stability: draw me a Lewis structure and it can be made. There are striking, yet understandable exceptions—small molecules for which you can draw a Lewis structure, but which have so far eluded synthesis. We can think of molecules such as cyclic ozone (**14**), dicarbon dioxide (**15**, OCCO), hexaazabenzene (**16**), and hexaprismane (**17**, Scheme 5). From each of these potentially transgressive molecules we learn something:

Cyclic ozone **14** is unstable relative to normal ozone by $\approx 30 \text{ kcal mol}^{-1}$ (all those lone pairs crammed into a small space). But it has a substantial calculated barrier to falling apart into its open isomer, because that process is a forbidden reaction.^[41]

OCCO **15** is a dimer of carbon monoxide, and that would explain, it might seem, its non-existence. But hold on, it should have a triplet ground state,

for the same reasons that O_2 has.^[42] And that may (or may not) make a difference.

Hexaazabenzene (**16**), cyclic N_6 , is computed to decompose with a tiny barrier to three N_2 molecules.^[43] Fine, that's an allowed reaction. But so is benzene to three $\text{HC}\equiv\text{CH}$ molecules; the same and not the same.

We note that the first three molecules in our list are perceived as problems mainly from the perspective of our impoverished representations. Lewis structures, otherwise a remarkably effective heuristic tool in chemistry, do not describe well the impediments to persistence that face (or protect) these molecules. For that, a quantum mechanical perspective is needed.

Then there is (or isn't) hexaprismane, **17**. The molecule should possess a strong tendency to dissociate into its two halves, two benzenes rings—the tiles discussed earlier!—however, we would also expect a substantial kinetic barrier here since the cleavage of a cyclobutane ring in such a cage molecule is a forbidden process. It is our limited synthetic methodology that so far has prevented the preparation of this molecule, not its (presumably) excessive strain.^[44]

Let us look at how another field uses extremes, and then return to chemistry.

Why Probe Limits? Philosophy

An interest in extremes characterizes that jewel of contemplation, philosophy. In logic, for instance, paradoxes play a special role—the Cretan who always lies, or Zeno's paradox, for example. Philosophical texts across the discipline consistently take up arcane conundrums at the periphery of their fields, testing in excruciating detail the strength of definitions. And not just in philosophy—the famous Einstein, Podolsky, and Rosen paper probed the limits of the paradigmatic Copenhagen formulation of quantum mechanics.^[45]

Philosophers relish gedanken experiments that set up constrained or extreme conditions and use these to clarify a concept. We quote here first two amusing (and influential) examples of this genre from the philosophy of mind; chemistry figures in both.

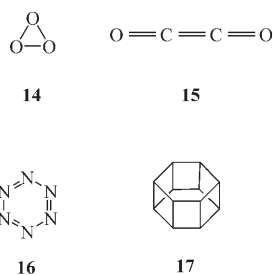
In an influential 1973 paper, Hilary Putnam tells the following story: "...we shall suppose that somewhere there is a planet we shall call *Twin Earth*. *Twin Earth* is very much like *Earth*: in fact, people on *Twin Earth* even speak English... One of the peculiarities of *Twin Earth* is that the liquid called 'water' is not H_2O but a different liquid whose chemical formula is very long and complicated. We can abbreviate this chemical formula simply as XYZ and suppose that XYZ is indistinguishable from water at normal temperatures and pressures."^[46]

Putnam's story goes on in some detail. Assuming that *Twin Earthlings* call XYZ "water" in their English, he then asks whether when an earthling, say Oscar, and his twin on *Twin Earth* say "water" do they mean the same thing? For Putnam's response, and how he used it to shape a position called "externalism," you will have to read his paper.^[46]

Another round in the debate that followed Putnam's paper used more chemistry in a gedanken-experiment mode, vide Donald Davidson's *Swampman*. Davidson goes hiking in a swamp: "Suppose lightning strikes a dead tree in a swamp; I am standing nearby. My body is reduced to its elements, while entirely by coincidence (and out of different molecules) the tree is turned into my physical replica. My replica, *The Swampman*, moves exactly as I did; according to its nature it departs the swamp, encounters and seems to recognize my friends. It moves into my house and seems to write articles on radical interpretation. No one can tell the difference."^[47]

Chemical practice might have something to say about the plausibility of these arguments, but we are not going to go there. The scenarios of *Twin Earth* and *Swampman* definitely help philosophers sharpen their ideas, as distorted molecules help the chemist.

Ethics is replete with constructed dilemmas that illuminate. Here is Philippa Foot's *Trolley Problem*: "[Supposing that a person] is the driver of a runaway tram which he can only steer from one narrow track on to another; five men are working on one track and one man on the other; anyone on the track he enters will be killed."^[48]



Scheme 5. Can you make a compound when you can draw its Lewis structure?

Which track should he steer to? The Wikipedia article on *The Trolley Problem* describes a number of ingenious variations on this problem. A general (and recommended) strategy for discussing the ethics of any action is to set up a range of cases, so to clarify for oneself what the criteria for action might be.

At times, philosophy's concern with strange exceptions makes one want to scream: "You are obsessed with the periphery; think about the center!" But considering extremes is often the most direct way to challenge accepted, yet perhaps not well-thought-through notions. The fringes are a frame; they define the center.

Vexing Nature

In a seminal text of the ideology of science, "*Of the Advancement of Learning*," Francis Bacon writes in 1605: "*For like a man's disposition is never well known till he be crossed, nor Proteus ever changed shapes till he was straitened and held fast; so the passages and variations of nature cannot appear so fully in the liberty of nature, as in the trials and vexations of art.*"^[49]

By "art" Bacon here means experiment. And he repeats the argument for interrogating nature through experiment in his 1620 *Novum Organum*.

The potential connection to sadism is clear. In a discussion of the Protean metaphor and the tension of "invasive" (destructive?) and "noninvasive" (non-destructive?) techniques in chemical experimentation, Pierre Laszlo and one of the authors write elsewhere: "*Bacon was accused of being the first of a long series of villains to 'put nature on the rack,' a rationalizer of torture in the service of science. Goethe's revulsion at Newton's incarcerating passage of light through a slit (and its subsequent analysis into the component colors by a prism) is emblematic. As are Donne, Wordsworth and Ruskin's impassioned denouncements of science and of the attendant industrial revolution. The line continues, to some (hardly all) of the environmentalist and animal rights critiques of the interventionist nature of science.*"^[50]

The tickling of a molecule to get it to send us signals from within may be very, very light. No bonds are made or

broken. But the quantum strings must be plucked. Chemical experiment so often reaches beyond analysis, and thrives on perturbation and intervention. And if we left things where they were, there would be no chemical industry. For real change is effected by perturbing equilibrium, by transforming the natural. In art as well as science.

Extreme Conditions

Another way in which the normal is perturbed in science is by exposing matter to extreme conditions—high or low pressure or temperature, high magnetic or electric fields, high levels of radiation, extreme salinity or concentrations of one or another chemical. Heating, of course, is at the heart of chemistry. One could not imagine our science without the motive force of first fire, and then its surrogates. Yet extreme heating does away with chemistry; molecules don't have a life on the surface of the sun. On the other hand, low temperature turns off entropy, so to speak. The temperature range of existence of that marvel of systems chemistry, terrestrial life, is wider than we think. We continue to be surprised by extremophiles that flourish at temperatures higher than that of boiling water at 1 atm and lower than that of freezing water. The strategies life adopts under extreme conditions are just fascinating, from anti-freeze proteins, to the lipids of thermophiles, to the repair mechanisms of *Deinococcus radiodurans*.

Each set of circumstances has interesting consequences for physics, chemistry, and life. Let's discuss in detail one of these, high pressure, a field which one of the authors has recently entered.^[51] High pressures are the norm in the interior of planets. Such pressures can also be attained in controlled fashion in the laboratory, between diamond anvils. The only imperative under high pressure is "get denser." The average dimensions of a crystal may shrink by a linear factor of 1.7, and the *PV* term in the enthalpy of any reaction approaches 10 eV at pressures of the order of 350 GPa (greater than the strength of any bond).

Here are some of the incredible things that happen at high pressure: Everything eventually turns metallic. In

the range of pressures accessible in the laboratory people have made Xe metallic. Iodine also becomes metallic under pressure, and the diatomic bonds "dissolve" into square sheets of I atoms. Not yet NaCl, but CsI and BaTe, pretty ionic solids, can be metallized.

If not metallization, there is coordination alchemy under high pressure. Two of our best thermodynamic sinks, CO₂ and N₂, are transformed at high pressure into structures resembling forms of quartz and elemental P or As, respectively. The advantage of multiple bonding gives in to the necessity of compactification. If someone insists on cramming you in tighter than sardines in a can, then you had better form as many bonds as possible with your neighbors.^[51]

Even our cherished notion of close-packing, as obvious to the sellers of oranges in ancient Egypt as to us, has to be modified. Every alkali metal and alkaline-earth element under pressure has been shown in the last decade to go out of the familiar close-packed *hcp* or *fcc* structures into incommensurate and commensurate not-close-packed (but denser) structures.

What's normal depends on the niche, and your perspective—the center of the earth (not to speak of that of Jupiter) is not the world of 1 atm. And squeezing the hell out of molecules is hardly sadistic—it leads to new chemistry, new ideas. Obviously, our understanding of molecules under high pressure probes the state of our understanding of molecules under ambient conditions.

Mastery

It could be that the central role of synthesis in chemistry is related to the desire to make unusual molecules. To make such molecules is, of course, far from the only reason people make compounds, whether it is those occurring in nature, or unnatural ones. Molecules were synthesized in the past to confirm analysis, that is, to show that the scant clues as to their structure were interpreted correctly. Today they are more often made because they may display a function of interest or because they may provide a starting material for the usual medicinal chemical exploration.

tion of increasing activity and decreasing toxicity. They may be made simply because they are the Everests of evolutionary complexity in nature. Berson has written cogently of all the non-Popperian reasons for making molecules.^[52]

All the time, in organic chemistry classes, our apprentices are asked to design syntheses. As we pointed out in a previous section and above, there are many reasons, psychological, intellectual, and aesthetic, for this fundamental chemical activity. But making molecules, natural or unnatural, is the way our understanding of nature is demonstrated.

The easy ones are made first, then increasingly more difficult ones. It makes sense that the goalposts be always placed further away—more complex, more asymmetric centers if it is a natural product, less stable if one has in mind an unnatural product. In an experimental science, especially in the science where making it is paramount, the very human desire to understand is quite naturally parlayed into a search for the extreme.

Not that this outlook is without a certain measure of human arrogance. Alain Sevin has put it well: “*The incredible richness and fantasy of Nature is an act of defiance to Man, as if he had to do better in any domain. Flying faster than birds, diving deeper than whales... We are promethean characters in an endless play which is now in its molecular act.*”^[53]

Liberté

We have laid out some of the intellectual motives for preparing “borderline”, or even “beyond-the-pale” molecules. But the urge to reach the extreme goes deeper, to our origins. It paid to be an extremist—the faster runner, the healthier mother, the better hunter—and their offspring had the better chance to survive, especially when the niche changed. Deviance, the father of existence under extreme conditions, is thus absolutely essential for evolution.

Society needs border crossing too, for knowledge evolves, just as organisms do. And the economies of the world, and our ability to deal with the crises of our own doing, depend on innovation.

Transgressive (yet ethical) research should not only be tolerated, but actively embraced. Support is needed for way-out research projects that apparently do not lead to application. The periphery is the zone where innovation occurs. And it is the rim from which we understand the center better: normality in all its importance, but also in its limitations.

It is said that the Marquis de Sade shouting from his cell played a small role in inciting the assault on the Bastille. The slogans of the French Revolution—*Liberté, Égalité, Fraternité*—actually provide a better guide than Sade’s vision. They carry in them the tension of human creation: the normal, and common good, in contention with individual freedom. The desire to make the molecule that violates the norm is part of that human struggle.

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