depressed patients. McEwen says one role of antidepressant treatments may be to interrupt this negative sequence of events and restore normality of steroid levels and the adapative response to them.

Delgado believes both human and animal research is converging to suggest that scientists "are on the right track"—the track that leads to the final common pathway. Electroconvulsive therapy (ECT) supplies another important road sign. Because it works rapidly and is 90% effective (according to Heninger), some researchers see it as the "gold standard" for treatment of depression. ECT seems to have the same effects on brain chemistry as do antidepressants—and investigators suspect it may work by actually altering gene transcription. Duman, for example, has found that a course of ECT will alter the responsivity of the proto-oncogene *c-fos* in rats.

Many clinicians are still wary of the procedure, which developed a scary reputation from early indiscriminate use, and side effects—namely memory loss—are a problem in some cases. Thus, what scientists would ideally like to find, says Heninger, is "a drug as effective as ECT." Sulser, for one, is optimistic. "We will probably come up with drugs that can bypass all these [transmitter and receptor] systems," he says. "If we can target the final common pathway we could ideally come up with a drug that directly affects gene expression"—presumably "the fast-acting antidepressant we are all looking for."

Sulser predicts, however, that in the foreseeable future, we are unlikely to see any new drugs that create a splash comparable to that generated by Prozac. Rather, we can expect continuing refinements of existing drugs, as well as possible improvements in therapy by combining those now in use. Yale researchers, for example, have tentative evidence showing that combining fluoxetine with desipramine produces faster results than either drug acting alone.

And in spite of all the hopes raised by the current work, not everyone believes that even the identification of a common pathway will lead to a silver bullet to slay all the dragons of depression. Post notes that different neurochemical systems—such as the dopamine system—may be involved in cases where patients don't respond to the usual drugs. Peptides—which may be involved in the positive effect sleep deprivation can have on depression—also need looking into. Thus, in Post's opinion, finding a faster-acting antidepressant "is not the key thing—the key thing is matching the patient with the right type of medication." But the recent inquiries into a final common pathway suggest that in the long run there will be better medications to match with patients. ■ CONSTANCE HOLDEN

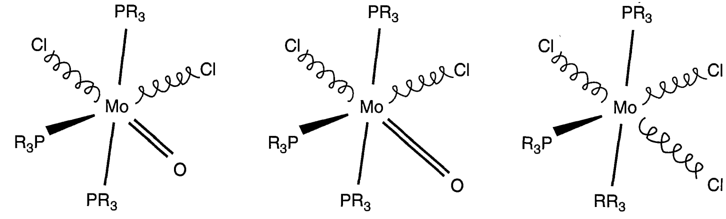
The Case of the Unlikely Molecular Twins

How molecules differing in nothing but a single bond's length almost became chemical orthodoxy

IN 1971, A TRIO OF CHEMISTS LED BY JOSEPH Chatt at the University of Sussex in England synthesized a pair of chemical twins too odd to remain anonymous. The chemists were convinced that the so-called transition-metal complexes they made had exactly the same chemical formula. But one of their chemical specimens formed sapphire-blue crystals, and the other bright green ones. That much is not so unusual in chemistry. Presumably the molecular doubles were isomers: forms of a compound in which the same atoms—molybdenum, oxygen, chlorine, phosphorus, carbon, and hydrogen, in this case—are linked into different molecular geometries. But if these compounds were isomers, they were isomers unlike any that chemists had encountered before.

X-ray structural analyses of the blue and green crystals showed that both compounds' atoms were in virtually the same relative positions. The only difference the chemists could discern in the data was one they had never come across in their training: The molybdenum-oxygen bond was strikingly longer in the green compound than in the blue one.

"I thought it was very peculiar," recalls Chatt, retired now for 12 years. "But it seemed to provide an explanation for the x-ray evidence." Chatt and his colleagues Ken Muir and Ljubica Manojlovic-Muir (a husband and wife team now at the University of Glasgow) called the unlikely twins "distortional isomers" and published their results in several British chemistry journals in 1971. The startling implication of the findings: Chemical isomers with strikingly different properties can differ structurally by nothing more than the length of a single bond.



Unlikely twins and an impostor. *The proposed bond-stretch isomers for the molybdenum complex, shown with the impostor* (right), *in which chlorine substitutes for the oxygen.*

SOURCE: PARKIN ILLUSTRATION: D. DEFRANCESCO

Thus began a saga that took as many twists and turns as a Nabokov novel before reaching a denouement just this past year. By 1985, distortional isomers seemed on the fast track to becoming chemical orthodoxy. But a spate of papers in the past few months have attacked both the experimental evidence for distortional isomers and an influential theoretical account of how they could exist. Many (but not all) of the chemists who thought the evidence for distortional isomers was approaching textbook solidity are now acknowledging that they were thrown off by impurities—about the last thing they expected in well-formed crystals like Chatt's original twins.

The notion of distortional isomers was slow to take hold, perhaps because it is so counterintuitive. Chemists sometimes think of bonds as springs, with a characteristic length. Distortional isomers presented a very different picture, remarks Gerard Parkin, a chemist at Columbia University and one of the most influential researchers in the field. "It's like having a spring attached to the ceiling, which had always bounced up to your face when you released it from the floor, but this time it bounced above your head," Parkin says.

Rather than accept that unsettling possibility, most chemists quietly discounted the Sussex researchers' results, says Nobel Prize–winning chemist Roald Hoffmann of Cornell University. "Nobody was interested in trying to reproduce their results, probably because people thought they got something wrong about the compounds' structures," Hoffmann recalls. Besides, he adds, it usually takes more than one lab reporting one anomalous result to get theorists seriously thinking about explanations.

The requisite second anomaly arrived in 1985 when Karl Wieghardt and colleagues at the Ruhr University in Bochum, Germany, reported in the journal *Angewandte Chemie* that they had found another pair of distortional isomers: blue and green crystals from tungsten-containing complexes. Like the Sussex examples, the crystals seemed chemically and structurally identical—except in the lengths of one metal-oxygen bond.

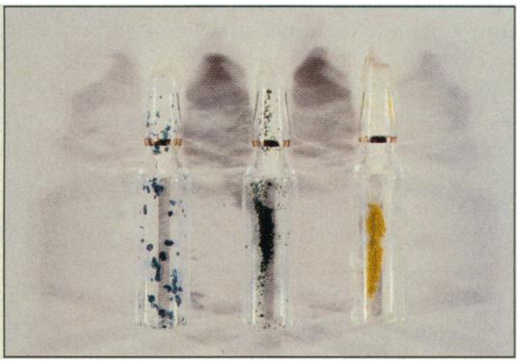
Since then several other cases have been registered in the literature, but the German work was enough to get theorists, including Hoffmann and workers at the University of Chicago and the University of Paris, talking seriously about the phenomenon. To Hoffmann, the conundrum was irresistible. "I collect anomalies," he says. In 1988he and his colleagues published a theory to explain the oddity, which they renamed "bond stretch isomerism," in the *Journal of the American Chemical Society*. They suggested mechanisms by which certain electrons associated with the metal atoms in these transition-metal complexes could take on two distinct states that were comparable in energy—but were expressed in bonds of very different lengths.

With several apparently reliable observations of bond-stretch isomers and an explanation for how they might arise by top-notch theorists, the new kind of isomerism seemed on the way to becoming received wisdom. "The Hoffmann paper legitimized it" for many chemists, recalls University of Arizona chemist John H. Enemark, who has 20 years of experience with molybdenum chemistry. This year, in fact, a new inorganic chemistry textbook contained a discussion of the phenomenon.

But that may prove to be the idea's high-water mark. Soon after the Hoffmann paper, Enemark gave a graduate student the task of reinvestigating Chatt's original molybdenum complexes to learn more about the phenomenon. Enemark also began a collaboration with Wieghardt to unravel details of the tungsten complexes the German group had studied. At about the same time, Columbia's Parkin began probing the phenomenon, again focusing on molybdenum complexes similar to Chatt's.

Parkin's team was the first to publish bubble-bursting findings, in the 13 February *Journal of the American Chemical Society*. Instead of making two sets of crystals, green and blue, the group harvested a single crystal whose smallest structural unit seemed to contain both the long and short bond-stretch isomers. "This was a great chance to study both molecules at the same time," Parkin recalls thinking. But though the x-ray data seemed to bear out Chatt's original finding of two different bond lengths, another technique, infrared absorption spectroscopy, suggested that the crystal hosted only a single kind of molybdenum-oxygen bond.

Suspecting they may have botched the sample preparation step, the Columbia researchers resynthesized and recrystallized their experimental compound. As before, the x-ray analyses indicated a pair of molybdenum-oxygen bonds of different lengths. But this time the bond lengths were different from those of the first crystal. Taken at face value, the findings suggested, implausibly, that the molybdenum complex could assume four different bond-stretch isomers. "At that stage, I realized something was wrong," Parkin says.


ENEMARK ET AL.

Tainted beauty. *Pure crystals of a molybdenum complex are transformed from blue to green by a trace of the yellow impostor.*

In short order, the researchers pinpointed their problem. They found that their crystals were tainted with a chemical impostor. It seemed that during the sample preparation, a chlorine atom sometimes substituted for the main product's oxygen atom, creating an unexpected impurity. When the pure blue compound co-crystallized with the impurity, which is yellow, high-quality green crystals were the result. And because the chlorine-metal bond is longer than the oxygen-metal bond, the presence of the impurity also explained the "isomers." X-ray structural analysis of the tainted crystals averaged the oxygen-metal bonds with the longer chlorine-metal bonds, skewing the apparent bond lengths.

"This is a problem that you cannot solve by x-ray crystallography alone," agrees Enemark, whose group did an independent reexamination of molybdenum complexes. He and his colleagues used a battery of up-to-date spectroscopic techniques to probe the samples' chemical compositions, bond types, and structures. They too found undeniable signs of the impurity, but it wasn't easy even with refined analytical techniques. "All this shows that it would have been difficult [for Chatt's group] to have known that the green crystal was a mixture of the blue and the yellow [complexes]," Enemark says.

To find out just how Chatt's group was misled, Parkin's team systematically made crystals of molybdenum complexes doped with different amounts of the yellow compound and did x-ray analyses of them. Based on the results, Parkin says it is likely that Chatt's green crystals contained several percent of the impurity—enough to stretch the apparent length of the oxygen-metal bond by the amount Chatt's team reported.

Chatt now concedes that his group was led astray, largely because of their assumption that the single well-formed crystals they were working with contained only one molybdenum compound. The case for bond-length isomerism in the tungsten clusters has also crumbled: Based on the reanalysis he did with Enemark, Wieghardt admits that he and his colleagues were victims of a similar contamination scenario.

Even the theoretical hope for bond-stretch isomers came under attack last month in the journal *Inorganic Chemistry* when Michael B. Hall and Jun Song of Texas A&M University reported that their supercomputer calculations failed to agree with the results of the earlier theory paper by Hoffmann and his colleagues. But Hoffmann isn't convinced that Hall and Song's refutation is airtight. "The experiments have been proven wrong," he says, "but the explanation hasn't been."

That would seem to leave Hoffmann's explanation looking for an event to explain. But chemists Vernon Gibson of the University of Durham, Mary McPartlin of the Polytechnic of North London, and their colleagues may have made the search easy. Working with niobium-containing complexes, they reported two new sets of candidate bond-stretch isomers in the August *Angewandte Chemie* (English edition). One of the complexes, they propose, can form both green and yellow crystals differing only in the lengths of their niobium-oxygen bonds; the other can grow into orange and green crystals distinguished by their niobium-sulfur bonds.

Some of this new evidence for bond-length variations comes from x-ray data, which McPartlin concedes may not be reliable. But she also sees signs of varying bond lengths in the crystals' infrared spectra. "We can't explain [the spectra] any other way," she says. Parkin argues, however, that such shifts could easily come from unidentified contamination. Bond-stretch isomerism, he says, is as likely as "life on Mars."

Regardless of the fate of bond-stretch isomerism, its 20-year history serves as a reminder that errors lurk in the most unsuspected places, Enemark says. The assumption—plausible in 1971, still common today, and always risky—that single well-formed crystals are unlikely to harbor impurities opened the way to "findings" that nearly ushered bond-stretch isomerism into accepted theory. That's a salutary lesson, says Hoffmann—and it has raised as a theoretical possibility a new phenomenon that he thinks may still be realized. "This is how science should work," he says. ■ IVAN AMATO