Abstractions

SENIOR AUTHOR

For nearly 70 years, a tiny organic compound called 2-quinuclidone has baffled organic chemists: no one could definitively synthesize it.

Brian Stoltz, a chemist at the California Institute of Technology, Pasadena, took on the challenge after repeatedly encountering the enigmatic molecule, which does not occur naturally, in the early years of his career. He first learned of 2-quinuclidone as a graduate student, while house-sitting for Yale University chemist Harry Wasserman (see page 699). It is a molecule in which the amide bond in its constituent amino acid is twisted out of shape. Wasserman said it deserved further study; Stoltz made a mental note.

Later, and without prompting, Stoltz's postdoc mentor Elias Corey identified 2-quinuclidone as a "classic unsolved problem in synthesis". When he became an independent investigator, Stoltz began his quest. He devised an unambiguous path to the molecule that was confirmed by X-ray crystallography, and tells *Nature* about it here.

Why was the compound so difficult to make?

The structure is very twisted, and predicted to be very unstable. That's presumably why chemists in the 1950s and 1960s were unable to make it.

How did you succeed where others failed?

Every previous approach to the compound started from an amino acid, and then tried to build the last ring by making a nitrogen–carbon bond. But the instability of this bond meant that if water contaminated the product, it would decompose to the amino acid and you would never know that you had succeeded.

We wanted to devise a synthesis whose result would be completely unambiguous even if you got water into the system. We constructed the rings using a different bond from the one that breaks on decomposition.

Does the work simply resolve a historical oddity, or are there practical implications?

Both. Some think these twisted amides are prevalent in biological systems. Maybe an enzyme could grab hold of a peptide in such a way that it twists the amide and makes it ready for cleavage.

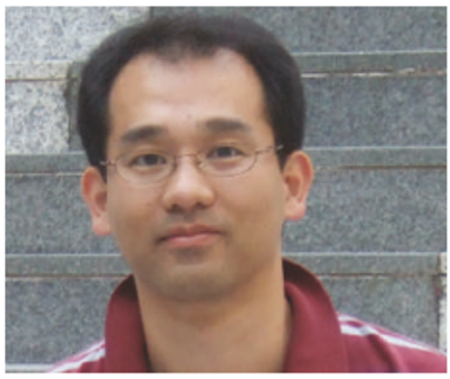
Was the X-ray crystallography crucial or did it just confirm what you found?

It would have been tough to convince me to submit the paper without the crystal structure, just because it had been such a controversial compound. The structure itself was reasonably routine, but the hard step was getting the crystals because the compound is so prone to decomposition. Kousuke Tani, the paper's first author and a postdoc of mine, had a fantastic feel for it.

MAKING THE PAPER

Kazuki Horikawa

Japanese scientists ask how embryos tell the time.



The bodies of most animals contain repeated segments, such as vertebrae or ribs. As the embryo develops, these units are laid out sequentially, from head to tail with impeccable timing.

Scientists have long known that expression goes up and down for many genes in cells of the pre-somitic mesoderm — the tissue in the vertebrate embryo from which segments arise. This oscillation in gene expression parallels the rhythm of segment formation, as if each cell were keeping time with an internal clock. But although much is known about the molecules that regulate oscillation inside each cell, scientists have not yet worked out how cells synchronize their clocks so that they all tick in unison.

Kazuki Horikawa took a two-pronged approach to this question. He and colleagues at the University of Tokyo in Japan put genetically engineered cells from the pre-somitic mesoderm into zebrafish embryos to monitor the effects of different molecular changes on segment formation and gene expression. At the same time, collaborators at Nagoya University constructed a mathematical model of the multicellular clock to predict how changes in one parameter would affect clock dynamics. As described on page 719, the teams took turns conducting virtual simulations and *in vivo* experiments, each process informing and validating the other.

In one set of experiments, Horikawa's team transplanted cells that kept producing a signal for the Notch receptor, a critical protein in many types of pattern formation. They found that the resulting embryos made smaller segments. The mathematical simulation predicted that an increase in a signal from one cell would drive its neighbours to tick faster, thereby reducing segment size. The experimental team confirmed that the phase of oscillation around the transplanted cells had indeed become quicker.

Once the researchers had validated the mathematical model experimentally, "we were able to carry out numerous virtual experiments," says Horikawa. One of the more successful examples investigated 'noise' generated by erratic cell division. Using high-resolution imaging techniques, Horikawa and colleagues had found that cells actively proliferate in the synchronized oscillation zone, even though it had long been assumed that cells there do not divide. The team showed that the process of cell division changes the timing of clocks in individual cells. The mathematical model predicted that Notch signalling is critical for overcoming the effects of such noise to ensure coherent oscillations among cells… and a series of experiments confirmed this.

The imaging techniques and transplantation experiment were technically difficult and took a long time to finesse. "But the most challenging and fruitful aspect of the work was the communication between the experimental team and the theoretical team, which are very different in their cultures," says Horikawa. "I believe that mixing these philosophies was the key to our success."

Now such a cooperative system is in place, Horikawa hopes to delve further into the mechanism of the clock. For example, he wants to find out how the synchronized oscillation is converted into segment boundaries. "Many questions remain to be answered." ■

QUANTIFIED **PEER REVIEW**

A numerical perspective on *Nature*.

Peer review is commonly accepted as an essential part of scientific publication, and yet there is no 'correct' model for it. *Nature*'s peer-review process has remained unchanged for decades. But the journal is open to alternative approaches and, to that end, has started a web debate and a peer-review trial.

The web debate brings together opinions from key people to explore current systems and viable alternatives. It addresses questions about the ethics, quality and value of peer review, as well as relating scientists' personal experiences (www.nature.com/nature/peerreview/debate).

The peer-review trial allows authors to post submissions on a preprint server for comment from anyone in the field (blogs.nature.com/nature/peerreview/trial). Editors will note all comments and invite authors to respond.

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9,571 reviews were done for *Nature* last year (including multiple rounds).

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