



# Mirror Molecules

In the chemistry of life, left-handed amino acids are the rule. Why does nature make so many exceptions?

*By Sarah Everts*

**I**RRITATE A MALE PLATYPUS DURING BREEDING season, and you may end up trapped by its stumpy hind legs, threatened by a set of sharp spurs that are armed with venom. The painful poison hobbles male competitors and is a handy defense against pesky humans and dogs. It is also a somewhat odd concoction, as might be expected from a mammal that is famous for its egg-laying, duck-billed weirdness. Platypus venom contains a class of molecules that biologists once thought did not occur naturally outside the microscopic world of bacteria.

Those molecules are mirror images of the amino acids that cells normally string together to make all of life's proteins, which are vital to proper functioning. The mirror images are composed of the same atoms that make up the 20 or so standard amino acids in biology's tool kit, and the atoms are attached to one another in the same order. Yet the orientation of the attachments diverges slightly, resulting in structures that differ from classic amino acids in much the way a right hand differs from a left hand. The two forms are not, however, interchangeable in biological reactions. Indeed, classic amino acids are now referred to as left-handed, and their mirror images are said to be right-handed.

## IN BRIEF

**Amino acids**, the building blocks of proteins, can adopt forms that, like our right and left hands, are mirror images of each other. When life arose on the earth, it favored so-called left-handed amino acids over right-handed ones to carry out cellular activities.

**For a long time** the only exceptions to this pat-

tern were found in bacteria. In recent years, though, more and more examples have been found in higher organisms, including humans.

**Biomedical researchers** are studying applications of the exotic amino acids to treat medical conditions, such as schizophrenia, cystic fibrosis and macular degeneration.

Right-handed amino acids were once assumed to play a minimal role in higher organisms because they would be mismatched to, and thus unable to work in, the molecular machinery of most plants and animals. In recent years, however, biologically active right-handers have been turning up in all kinds of unexpected places—from substances that lobsters produce to initiate sex to a hallucinogenic drug used by indigenous hunters in Peru. Most intriguingly, right-handed amino acids have been found to perform important jobs in human physiology, and they hold exciting potential for the development of new treatments, including for cystic fibrosis, schizophrenia and macular degeneration.

Solomon Snyder, a neuroscientist at Johns Hopkins University who did much of the early research into the function of right-handed amino acids in the brain, says he met considerable resistance when he tried to publish his first papers on the subject. Yet to him, the chemicals were intriguing precisely because they seemed to “break the first rule of mammalian biology,” as he puts it. “Like most of science, whenever there is something really new or different, some people say, ‘That’s ridiculous.’”

As it happens, flipping a left-handed amino acid into its mirror image often takes just a few simple steps, biochemically speaking. Thus, it was probably inevitable that evolution would experiment with making right-handed amino acids. “Nature was clever enough to use them all these years,” says Richard Losick, a cell biologist at Harvard Medical School. “We were just slow to realize it.”

#### A USEFUL ACCIDENT

HOW IS IT that left-handed amino acids came to predominate over their right-handed siblings—so much so that the diverse biological functions of right-handed forms long escaped serious notice despite the molecules having been characterized in the late 1800s? Some scientists argue that the left-handers’ edge stems from the cosmological equivalent of a coin toss. The first chemical entities able to replicate themselves successfully just happened to use left-handed amino acids, and this bias was “grandfathered in,” suggests Robert Hazen, who is a geophysicist and origins-of-life researcher at George Mason University. Another popular theory holds that polarized light emanating from a rapidly rotating star in our primordial galaxy somehow selectively destroyed right-handed amino acids, improving the odds that left-handed amino acids would emerge as life’s building blocks. The two forms are also known as L-amino acids and D-amino acids, respectively, after the Latin words for left (*laevus*) and right (*dexter*).

Once the choice was established, evolution had a clear incentive to perpetuate a dominant amino acid, explains Gerald Joyce, who studies the origins of life at the Scripps Research Institute in La Jolla, Calif. “By analogy, the convention in Western countries is to greet people by shaking right hands. It would work just as well if we all agreed to shake left hands, but if there was no convention, then there would be many awkward encounters.” Thus, most of the machinery of living cells, from the enzymes that produce amino acids to the complex structures known as ribosomes, which string amino acids together to form proteins, is compatible only with L-amino acids and not with their D counterparts.

Indeed, the early decision by life to favor left-handed amino acids may have influenced the “handedness” of another class of organic compounds—the carbohydrates. Many research groups in the past decade have demonstrated that the predominance of

**Sarah Everts**, a native of Montreal, is the Berlin correspondent for the weekly magazine *Chemical & Engineering News*. She also blogs about art and science at Artful Science.



certain simple left-handed amino acids in experimental solutions that mimic the primordial soup that may have existed on the earth four billion years ago tends to favor, for complex chemical reasons, the formation of right-handed carbohydrates, which is in fact the orientation seen throughout the biological realm.

The exceptions to the left-handed rule for natural amino acids gained wider attention in the 1990s, after Snyder showed that some right-handed compounds serve as neurotransmitters in the human brain. In 2002 Philip Kuchel, a chemist at the University of Sydney, determined that platypus poison contains D-amino acids. In 2009 researchers at Harvard and the Howard Hughes Medical Institute reported that several D-amino acids performed new and unexpected functions in bacterial cell walls. By 2010 investigators were finding that complex assemblies of bacteria that spread out in films over various surfaces—from hot springs to medical equipment—seemed to be using D-amino acids as a cue for when the biofilms should disperse.

In humans, the amino acid D-aspartate has been shown to be a neurotransmitter that is involved in normal brain development. Meanwhile D-serine teams up with the L-amino acid glutamate to co-activate neuronal molecules essential to what neuroscientists call synaptic plasticity—a property that is, in turn, key to learning and forming memories. D-serine also seems to be an important factor in the multifaceted disorder schizophrenia. People suffering from the disease have lower quantities of D-serine in their brain, a finding that has inspired drug companies to look for ways to top up D-serine levels as a possible treatment. Too much D-serine, however, can cause problems in other circumstances. For those suffering from a stroke, an overabundance can lead to increased brain damage. So researchers are also trying to develop drugs that decrease D-serine levels to mitigate a stroke’s harmful consequences.

Our cellular factories produce only L-amino acids, so how, researchers wondered, do we end up having D-amino acids as well? Snyder found that brain cells do not build D-serine from scratch. Instead they make an enzyme that flips the handedness of the amino acid serine from its L form to its D form. That is a nifty way to capitalize on the abundant levels of L-amino acids already available in the cell.

Life employs the same strategy when a D-amino acid is part of a peptide—a small chain of amino acids—such as in platypus venom. In these cases, the trusty ribosome builds up the peptide from regular L-amino acids. Then an enzyme tweaks one of the individual amino acids in the chain to flip the L form into its D alter ego. By piggybacking on the machinery for making or connecting L-amino acids, nature does not need to evolve the entire team of right-handed biosynthetic enzymes that would normally be required to build a right-handed molecule, explains Günther Kreil, a chemist at the Austrian Academy of Sciences in Vienna, who in 2005 found an enzyme that poisonous South American

tree frogs use to make the D-amino acids found in their venom.

Kreil became interested in tree frog venom when he first heard of an indigenous people in Peru, called the Matsés, who exploit peptides containing D-amino acids that are found on the skin of a tree frog called *Phyllomedusa bicolor* as potent hallucinogens in their hunting rituals. The Matsés first burn their chests and then apply the frog skin extract to their singed wounds, which induces in them immediate diarrhea and heart palpitations before briefly knocking them out. When they awake, they have heightened senses and a feeling of superhuman strength. The frog peptide is almost entirely composed of L-amino acids, but without the single D-amino acid in the peptide, the drug has no hallucinogenic effect, Kreil says.

### SHADOW WORLD

ALTHOUGH D-amino acids show up in the poisons of a wide range of organisms, in other creatures the molecules have more peaceful purposes. Lobsters, for example, use D-amino acids for catalyzing romance and to keep their salt levels in order.

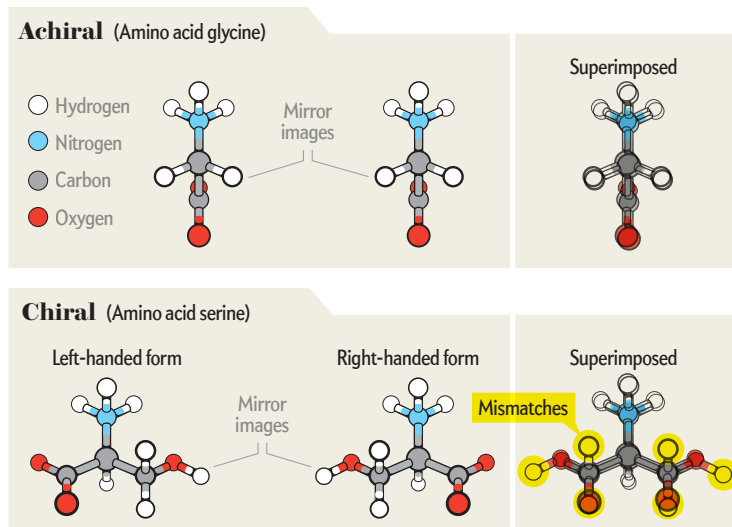
Yet the biggest users of D-amino acids are still microbes—although even here researchers are discovering new functions for the right-handed molecules. Most bacteria build their cell walls out of a sticky sugar-protein matrix called peptidoglycan, which is doctored with D-alanine and other D-amino acids. In 2009 Matthew Waldor of Harvard and Howard Hughes found that bacteria also reinforce the peptidoglycan with a mortar that includes D-methionine and D-leucine. These D-amino acids can also remodel the peptidoglycan of bacterial neighbors—even across species—a discovery that suggests, Waldor says, that the microorganisms may use the molecules to coordinate activities such as turning on fluorescence or building a biofilm. Understanding how these bacteria exploit D-amino acids for communication is of tantalizing interest to those wanting to develop drugs or products that break up the biofilms on our teeth, in the lungs of cystic fibrosis patients, in fuel pipelines and in medical equipment such as catheters.

One reason that bacteria and poisonous creatures employ D-amino acids is that when they are present in a peptide or a larger protein, they are not easily broken down by the enzymes of their host or enemy. All organisms have protease enzymes, whose job is to rapidly degrade and recycle L- but not D-amino acid proteins. In fact, drug developers have tried adding D-amino acids to therapeutic peptides and proteins to sidestep these janitorial proteases and thus enable drugs to last longer in the body.

Now that researchers are actively exploring this strange new world of right-handed amino acids, they are exploring additional roles that D-amino acids might play. Losick and others speculate, for example, that at least some of the D-amino acids produced by the trillions of bacterial cells that live on our skin, in our digestive tracts and elsewhere in the body may be im-

## How to Spot a Mirror Molecule

Of the 20-some amino acids in nature's standard tool kit, only glycine (*top*) is achiral, meaning it exhibits neither right-handed nor left-handed properties; mirror images of the molecule will exactly match each other if superimposed. The amino acid serine, in contrast, is chiral; its mirror images cannot be superimposed.



portant for human well-being, health and maybe even behavior.

One of the big questions in D-amino acid research now is whether any other part of the human body—besides the brain—actively makes D-amino acids. Preliminary evidence is suggestive. Yoko Nagata's group at Nihon University in Tokyo has reported D-amino acids in human saliva, while researchers led by Kenji Hamase of Kyushu University in Japan have observed D-alanine packed in high concentration in rats in the insulin-secreting beta cells of their pancreas. Also, in recent preliminary experiments in his laboratory in Australia, Kuchel has discovered enzymes in mouse and human hearts to convert L-amino acids into D-amino acids similar to the one in platypus venom.

What precise role such enzymes might play in human physiology, Kuchel says, is still, however, "a total mystery." At least the idea that they might have important functions no longer seems ridiculous. ■

### MORE TO EXPLORE

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