Features | Theoretical Chemistry

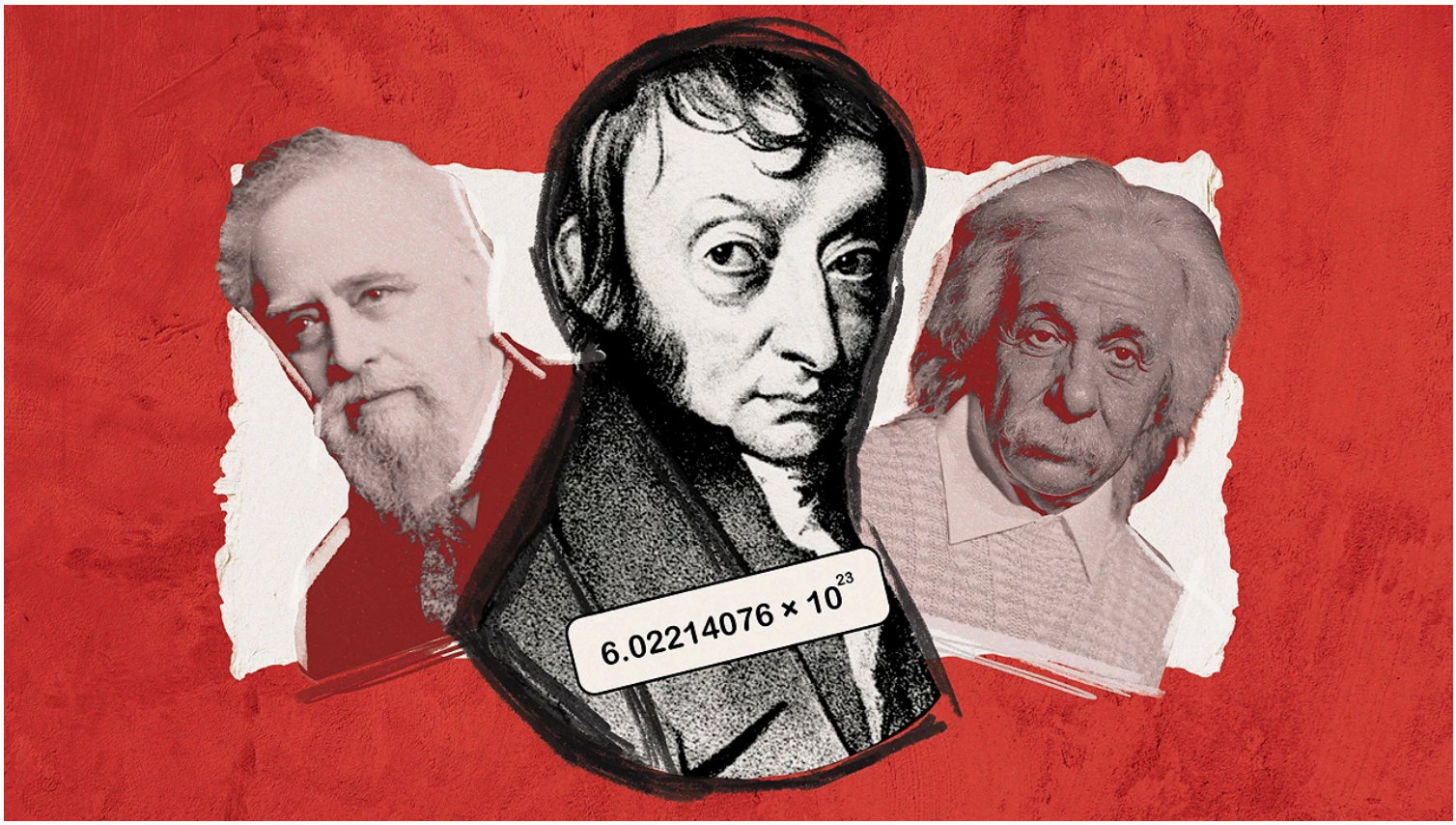
How Avogadro's number became constant

100 years ago, scientists proved that atoms really exist, and the famous 6×10^{23} number was settled

by **Ananya Palivela**

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KEY INSIGHTS

- Into the early 1900s, prominent scientists were unsure about the existence of atoms. Jean Perrin's calculations of Avogadro's constant convinced them that atoms are real.
- Pinning down the number took more than a century, from rough estimates in the 1800s to an exact, defined value in 2019, when the mole became a fixed count of particles.
- The movement of small particles, or Brownian motion, that Perrin measured to determine the number is still a working tool. Chemists use it to measure particles too small to see, including the nanoparticles that carry messenger RNA (mRNA) vaccines.

A little over a century ago, no one could prove that atoms exist.

Well into the early 1900s, some of the world's most respected chemists didn't believe that atoms were real. That concept, now so fundamental in science that most schoolchildren understand and accept it, was, back then, merely an assumption to simplify calculations for chemists.

Atomic theory was ultimately proven by a single number. The idea that proved it developed more than 200 years ago: if atoms truly exist, then a given amount of matter must contain a specific, countable number of them. And, in principle, that number should be quantifiable. In the early 1900s, Jean Perrin accomplished this by determining Avogadro's constant, settling the debate once and for all. His work confirmed that all things are made of atoms and earned him the Nobel Prize in Physics in 1926.

Avogadro's number—the number of particles in a mole—bridges the invisible world of atoms and the tangible substances we can measure, making it essential for every chemical recipe, drug dosage, and concentration calculation. It's so ubiquitous that it's sometimes called the "chemists' dozen." And every chemistry student memorizes its value: 6.02×10^{23}. After years of efforts to calculate the precise figure, Perrin finally succeeded by studying how tiny jittering particles move in a fluid.

"Perrin was someone with a microscope, a camera, and a clear understanding of what he was looking for," says Jhoan Toro-Mendoza, a scientific leadership adviser at the American Chemical Society. "His unbelievably simple experiment solved three important problems: it confirmed the existence of atoms and molecules, provided a way to measure Avogadro's constant, and created a method to study diffusion," he explains.

How Avogadro's number proved that atoms exist

“The idea of atoms started in Greek antiquity with philosophers who wondered about the ultimate composition of matter,” says Alan Rocke, a chemistry historian at Case Western Reserve University. “It was John Dalton who started the empirical chemical tradition of atoms, which was quite different from those philosophical ideas.” The philosophical notion posited that matter is made of tiny, indivisible pieces, while Dalton’s scientific idea proposed that each element has its own type of atom with a distinct weight.

But “Dalton’s atomic weights depended on molecular formulas, and in his day, no one could determine them. Water could be HO or H_2O,” Rocke says. “Both answers were reasonable at the time.”

> "Perrin was someone with a microscope, a camera, and a clear understanding of what he was looking for."
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> **Jhoan Toro-Mendoza**, scientific leadership adviser, American Chemical Society, on Nobel-winning physicist Jean Perrin

A few years later, in 1811, Italian physicist Amedeo Avogadro proposed a bold idea. He theorized that hydrogen and oxygen exist as pairs of atoms, what we now call diatomic molecules, that split apart during reactions. This theory explained why gases combine in neat ratios—two volumes of hydrogen and one of oxygen make two of water vapor. He was one of the first people to use the term *molecules* for combinations of atoms, stating that equal volumes of any gas at the same temperature and pressure contain equal numbers of molecules.

Avogadro never tried to estimate the number; he didn’t even name it. In fact, chemists at the time mostly ignored or rejected his work.

“There were people right from the start who agreed with Avogadro, but most scientists believed that there were problems with his theories,” Rocke says. “The rejection [of Avogadro’s ideas]

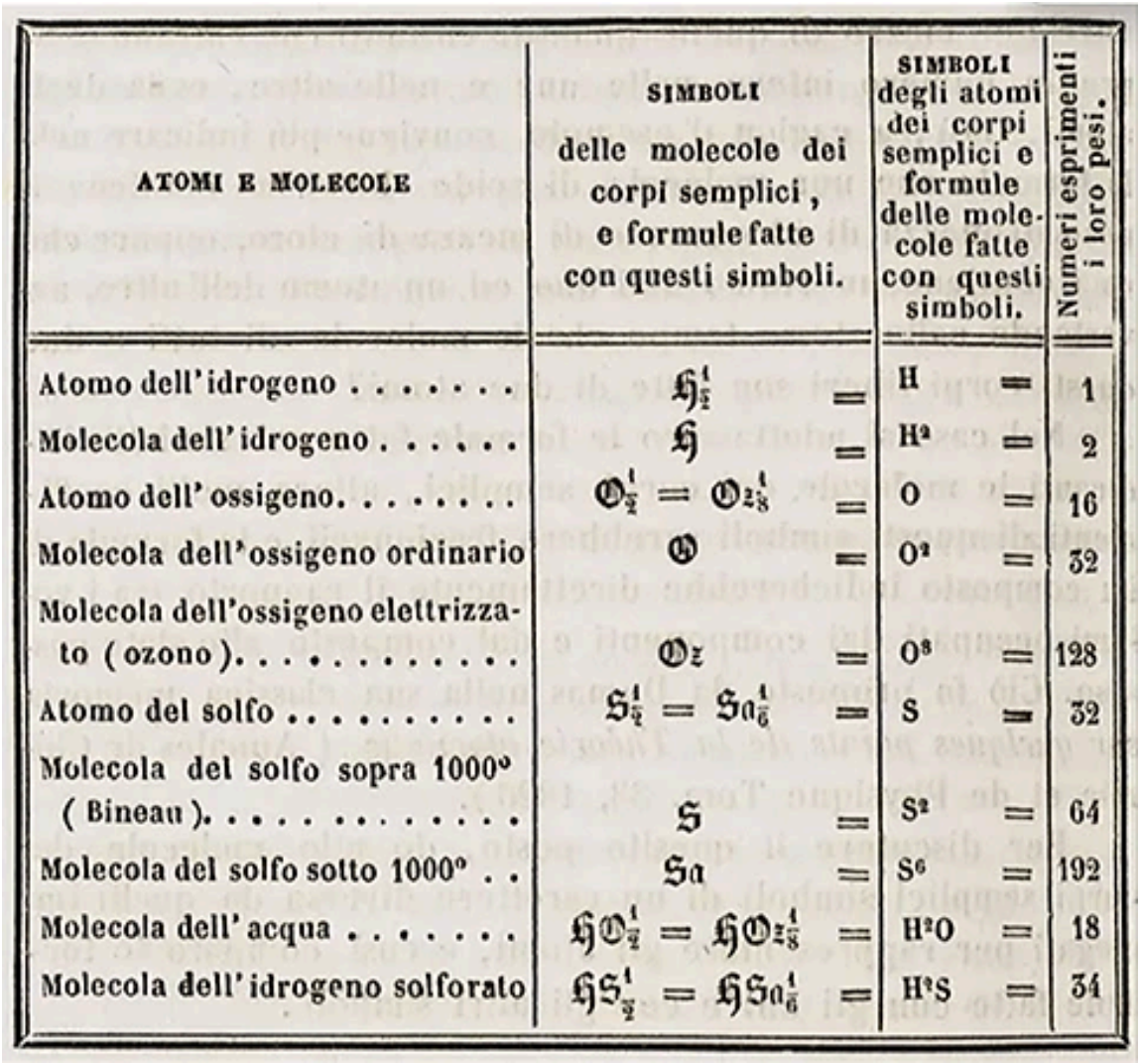
wasn't total foolishness; they had pretty good reasons that compelled a lot of really smart people throughout the 19th century."

Avogadro said two oxygen atoms join to form a molecule, and chemists asked the obvious question, Rocke says: "What could possibly hold two identical atoms together?" Scientists knew only two forces at the time—gravitational and electromagnetic, and neither fit as an answer to that question based on what they understood about how those forces work. "Avogadro ignored the question totally," Rocke says.

"There were also two philosophical ideas against the existence of atoms," he says. The first was a taste for simplicity. With about 80 known elements by 1900, scientists began to question why nature would be so complex, leading them to conclude that atoms might not be the indivisible fundamental particles that Dalton predicted them to be.

The second came from the Austrian physicist Ernst Mach and Baltic German chemist Wilhelm Ostwald, who both "turned their backs on atoms," Rocke says.

Mach was a positivist, says Krishna Choudhary, cohost of the science podcast *From First Principles*. "Positivism is the philosophy that the only thing that matters in science is the stuff that you can directly measure," he explains. Chemists can measure a substance in grams and liters, he says, but "you're not actually measuring atoms." So, in Ostwald and his supporters' view, atoms remained a useful theoretical tool for calculations and teaching but were ultimately unproven.



ATOMI E MOLECOLE	SIMBOLI delle molecole dei corpi semplici, e formule fatte con questi simboli.	SIMBOLI degli atomi dei corpi semplici e formule delle molecole fatte con questi simboli.	Numeri esprimenti i loro pesi.
Atomo dell'idrogeno	$\mathfrak{H}_{\frac{1}{2}}^{1} =$	$H =$	1
Molecola dell'idrogeno	$\mathfrak{H} =$	$H^2 =$	2
Atomo dell'ossigeno.	$\mathfrak{O}_{\frac{1}{2}}^{1} = \mathfrak{O}_{2\frac{1}{8}}^{1} =$	$O =$	16
Molecola dell'ossigeno ordinario	$\mathfrak{O} =$	$O^2 =$	32
Molecola dell'ossigeno elettrizzato (ozono).	$\mathfrak{O}_3 =$	$O^3 =$	128
Atomo del solfo	$\mathfrak{S}_{\frac{1}{2}}^{1} = \mathfrak{Sa}_{6}^{1} =$	$S =$	32
Molecola del solfo sopra 1000° (Bineau).	$\mathfrak{S} =$	$S^2 =$	64
Molecola del solfo sotto 1000° . .	$\mathfrak{Sa} =$	$S^6 =$	192
Molecola dell'acqua	$\mathfrak{HO}_{\frac{1}{2}}^{1} = \mathfrak{HO}_{2\frac{1}{8}}^{1} =$	$H^2O =$	18
Molecola dell'idrogeno solforato	$\mathfrak{HS}_{\frac{1}{2}}^{1} = \mathfrak{HSa}_{6}^{1} =$	$H^2S =$	34

Pamphlets of a seminal paper by Stanislao Cannizzaro, which includes this table, were handed out at a conference in Karlsruhe, Germany, in 1860. They showed how Avogadro's long-neglected hypothesis could give chemists unambiguous atomic weights. | Credit: The Linda Hall Science Library and Arboretum

Roughly 50 years after Avogadro published his theories, his ideas finally started to gain traction. "The famous story is the meeting at Karlsruhe," Rocke says, "where [Stanislao] Cannizzaro made a splash saying 'Avogadro was right, and you haven't taken him seriously enough.' "At the meeting, Cannizzaro distributed pamphlets that helped chemists agree on the values of atomic weights. These advances paved the way for Dmitri Mendeleev's periodic table, Rocke says.

Still, the number in Avogadro's law hadn't been accurately calculated. In 1865, Josef Loschmidt, a Viennese schoolteacher, made an attempt using the kinetic theory of gases to estimate the size of air molecules. The theory pictures a gas as countless molecules racing around and colliding. Loschmidt overestimated their size, which made his particle count an order of magnitude too small.

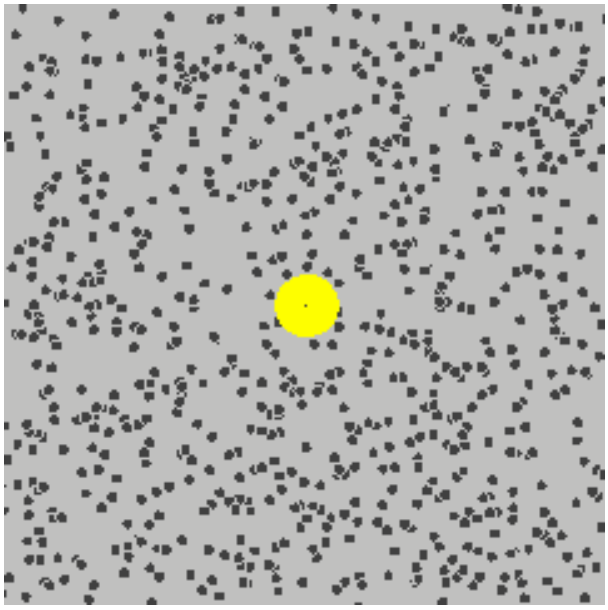
Eight years later, James Maxwell used his theory of gas diffusion and got much closer to today's value. And scientists continued to try to refine the number. But over the following decades, estimates ranged from about 4×10^{23} to 1.2×10^{24}, an uncertainty close to 100%.

This uncertainty fueled the ongoing debate. Ostwald introduced the term *mole*, defining it as a substance's molecular weight expressed in grams, decidedly different from today's definition. Ostwald's version focused solely on mass and did not address how many particles a mole contains. For chemists who shared Ostwald's skepticism about atoms, using the term *mole* allowed them to discuss chemical quantities without committing to the existence of discrete molecules. The definition was later revised to include a particle count.

Ostwald's *mole* definition was in line with the established laws of chemistry which, back then, only established mass ratios—for example, an oxygen atom weighs about 16 times as much as a hydrogen atom. But these laws alone could not prove that atoms exist. The mass ratios would remain unchanged even if every atom were a thousand or a billion times smaller, shrinking all the way to nothing. At that extreme, matter would appear smooth and continuous, making it impossible for chemistry to distinguish between discrete atoms and a seamless substance.

But if atoms were real, they'd have a definite size, so a given amount of stuff would hold a definite number of them. Divide the weight of a mole by that number—Avogadro's constant—and you get the weight of a single atom in grams. If Avogadro's number were a finite, measurable number consistent across various measurement methods, that would mean atoms truly exist.

Einstein's predictions and Perrin's measurements



This computer-simulated animation depicts Brownian motion. It shows how molecules (small black dots) in a fluid (black) can cause a larger particle (large yellow dot), such as a sphere of gamboge, to move in a zigzag path. | Credit: Wikimedia Commons

In 1905, Albert Einstein published four papers that changed science forever, Choudhary says. One of these papers was about Brownian motion, a phenomenon named after Scottish botanist Robert Brown, who watched tiny pollen particles drift in water under his microscope. He found that they continuously zigzagged without settling. Einstein developed an equation to describe this motion.

A tiny particle in water is constantly hit by water molecules from all sides. Since the impacts rarely balance out, the particle is pushed first one way, then another. Einstein predicted that the average distance such a particle moves depends on the fluid's temperature and viscosity, the particle's size, and Avogadro's number.

At the time, Einstein wasn't sure whether his predicted theory was the same as Brownian motion. He ended his paper with a call to experimenters to try to calculate Avogadro's constant. The experiment's results would not only prove the existence of atoms but also support fundamental theories about diffusion and particle motion under heat.

French physicist Jean Perrin took up the challenge. "He used this thing called gamboge, which is some kind of vegetable sap that comes from trees in India and Southeast Asia, and then he would rub the gamboge with his hands inside water," Choudhary says. "From that he could make very small particles, but the particles would be of all different sizes." He separated the spheres that were about a micrometer across by spinning them in a centrifuge.

"One of the reasons the experiment was so difficult was the preparation of very small particles of the same size and weight," Choudary says. He started with a kilogram of gamboge, and months of daily work left him with a few tenths of a gram of uniform spheres. "All of this was just to get the particles."

The spheres were large enough to see under a microscope and small enough for molecular kicks from water to toss them around. Perrin tested Einstein's prediction by following individual spheres under the microscope and marking their positions every 30 s. By plugging these

measurements into Einstein's equations, along with the water's known temperature and viscosity, Perrin solved for the only unknown: Avogadro's number.

He calculated the number in three other ways. He expected the molecular kicks to produce two other effects: in a drop of water, the spheres should settle into a layer that thins with height as gravity pulls them down; and a crowd of spheres should also gradually spread out through the water. How strongly each effect shows up depends on Avogadro's number, so Perrin used these effects to calculate the number in different ways.

The third method relied on a phenomenon Einstein predicted but didn't expect to be measurable: molecular kicks should not only push the spheres around but also spin them at random. But to Einstein's surprise, Perrin was able to measure this movement by growing spheres with tiny internal flaws that acted as markers to track their rotation. All four methods gave numerical values between about 6.5×10^{23} and 6.9×10^{23}.

"It doesn't surprise me that Einstein was surprised at the prowess of experimentalists," Choudhary says. "He spent his whole life being surprised by how good experimentalists were."

> "The simplicity of an experiment that novices can carry out is what really shows you the power of [Jean Perrin's] technique. "
>
> **Krishna Choudhary**, podcast cohost , From First Principles

Other scientists also estimated Avogadro's constant using methods unrelated to Brownian motion. They studied blue light scattered by the sky, the glow of hot objects, the electric charge of a single electron, and particles emitted by radioactive elements. Perrin compared his results with theirs, and all fell within the same range.

These results finally proved the existence of atoms with "a probability bordering on certainty," as Perrin put it in his 1913 book *Les Atomes*. Even ardent dissenters finally accepted the theory.

The Swedish chemist Theodor Svedberg was chasing the same goal. He used an ultramicroscope to track gold particles in water precisely. In 1911, his measurements gave values of about $6.2 \times 10^{23}$and 5.8×10^{23}, closer to today's value than Perrin's. Svedberg argued for years that he had been the first to prove the theory, but the consensus credits Perrin's experiments as decisive.

"There is evidence that Mach and Ostwald both conceded to the existence of atoms by 1910," Rocke says. Ostwald's doubts faded when scientists routinely saw particles from radioactive elements strike a screen.

In 1926, Perrin won the Nobel Prize in Physics for ending the long debate over whether atoms exist. The same year, Svedberg won the Nobel Prize in Chemistry for his work on such particle suspensions.

How many particles are in a mole?

What is the currently accepted value for Avogadro's number?

- ◯ 6.023×10^{23}
- ◯ 6.022×10^{23}

Even after he accepted that atoms were real, Ostwald never redefined the mole as a number of particles. A recent letter argues that if he had, chemists might have been spared difficulties with the definition that persist today (*J. Chem. Educ.* 2020, DOI: 10.1021/acs.jchemed.0c00421). Throughout the 20th century, the mole's reference stayed tied to mass. In 2019, that definition finally changed: a mole is now exactly $6.02214076 \times 10^{23}$ particles, and Avogadro's number is fixed.

An evergreen experiment

Today, a first-year university student can repeat Perrin's experiment. Choudhary did it as an assignment in his first computer science course at Princeton University. Students watched short movies of beads about a micrometer wide jittering in water, and then they wrote code to track each bead and measure how far it moved between frames. They used Einstein's equation to find Avogadro's constant. Choudhary recalls getting within about 2% of the accepted value. "The simplicity of an experiment that novices can carry out is what really shows you the power of that technique," he says.

Toro-Mendoza agrees. “The simplicity of that approach is so astonishing,” he says. It amplifies how theory and experiment can go hand in hand.

A century later, the jitter Perrin watched has become one of chemistry’s most useful tools. Chemists use a version of the experiment, a technique called dynamic light scattering, to size proteins, check whether antibody drugs are clumping, and confirm that the lipid nanoparticles carrying messenger RNA (mRNA) vaccines are the right size.

In his famous lectures, US physicist Richard Feynman declared that if all scientific knowledge were to disappear and just one bit could be saved, that bit should be the atomic hypothesis. One hundred years ago, Perrin proved that hypothesis while measuring Avogadro’s number and confirming Einstein’s explanation of Brownian motion along the way.



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