OBITUARY

Frank H. Westheimer (1912–2007)

Pioneering chemist at the interface with biology.

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Today, we recognize that the complexities of biology can be explained by understanding the chemical and physical properties of the molecules, both large and small, that interact to mediate life's processes. However, we should never forget the intellectual foundation that allows us to approach difficult biological problems in this way. Frank Westheimer, who died on 14 April at the age of 95, demonstrated that chemists have a unique advantage in deciphering the key processes of biology. Westheimer used his insight to describe the workings of enzyme-catalysed reactions, providing essential blueprints for future investigations of the biochemical foundations of life.

Westheimer was born in Baltimore, Maryland, on 15 January 1912. He graduated from Dartmouth College in 1932 and received his PhD in chemistry from Harvard University in 1935. Following a postdoctoral year at Columbia University, he joined the chemistry department at the University of Chicago, where he worked for nearly 20 years. However, this period was interrupted by the Second World War, when he was a supervisor at the National Explosives Research Laboratory. In 1953, he returned to Harvard, where he remained until his retirement in 1983. He received the US National Medal of Science in 1986.

Westheimer began his career as a physical organic chemist, and one of his most notable achievements in this area was the invention of molecular mechanics in the late 1940s. This is a mathematical approach in which the bending and stretching parameters of molecules are used to predict the rates of chemical reactions. The manual calculation efforts required were considerable, but molecular mechanics (and its sibling, quantum mechanics) is now used routinely as a computational method to predict the course of enzyme-catalysed reactions.

While at Chicago, Westheimer started working in biochemistry; he was the first to apply the rigorous analysis of physical organic chemistry to enzymes. Because he chose not to focus on a single problem, it is difficult to identify an area of biochemistry that Westheimer has not influenced. His first breakthrough was in the early 1950s, when he used isotopic labelling to study the oxidation of alcohol (ethanol) by the enzyme alcohol dehydrogenase. He discovered that a direct transfer of hydrogen occurs between the substrate and the enzyme cofactor — a then surprising result that demonstrated the power of his chemical approach. Today, this study could be simply performed using nuclear magnetic resonance (NMR) spectroscopy. But NMR wasn't available at the time, so Westheimer's analyses were accomplished by 'brute force': the organic molecules were combusted to produce water, which was converted to hydrogen gas. The isotopic content of that gas was then determined by mass spectrometry.

Westheimer also demonstrated that this enzymatic hydrogen transfer is stereospecific — the active site distinguishes between two chemically equivalent hydrogens in ethanol, transferring just one of them to the cofactor. Nowadays, it is understood that chemically equivalent hydrogen atoms in molecules can be differentiated in the chiral environment of an enzyme active site. But Westheimer's study was the first demonstration of this effect, and his results were unexpected.

Shortly after moving to Harvard, Westheimer went on to investigate another important class of biochemical transformation: phosphoryl transfer reactions. These are essential for many biological processes, including the production and use of metabolic energy, the storage of genetic information, and signal transduction. The central chemical event in these processes is the cleavage of bonds in phosphate ester molecules, which come in two varieties: monoesters (as found in the energy-storage molecule ATP) and diesters (such as those found in DNA). Westheimer established that the mechanisms of cleavage in phosphate diesters and monoesters are not the same, so providing a crucial understanding of how enzymes catalyse these diverse reactions.

With typical eclecticism, Westheimer made another ground-breaking discovery in the 1960s by determining how enzyme active sites stabilize carbanions — unstable organic anions that often occur as intermediates in enzyme-catalysed processes. Focusing on the reaction mediated by the acetoacetate decarboxylase enzyme, he showed that the carbanion intermediate is stabilized by a positively charged group (a β-iminium ion) that forms when the substrate reacts with a lysine amino acid side chain in the active site. He also established the importance of electrostatic effects in modulating the reactivities of chemical groups in active sites. In the case of acetoacetate decarboxylase, the active-site environment decreases the basicity of the essential lysine residue, a necessary effect if the enzyme is to work at neutral pH.

Westheimer continued to be intrigued by the cleavage of phosphate esters, and I joined his laboratory as a graduate student in the early 1970s as part of his research effort in that area. One day, I realized that I had inadvertently crystallized a crucial enzyme, so I asked Frank to come with me from his office to the microscope in the laboratory. Despite protestations that he was busy, he followed me, and I will never forget his smile when I told him what he was looking at. To a chemist, crystals are both measures of purity and objects of beauty. To Frank, crystals of a molecule as complex as an enzyme were a special joy.

Westheimer's achievements extended beyond academia. In 1965, he chaired the US National Academy of Sciences Committee for the Survey of Chemistry. This body issued the influential Westheimer Report, which recommended increases in US federal funding for the chemical sciences and highlighted the importance of the emerging field of biochemistry. Westheimer also served as a science adviser to US President Lyndon Johnson from 1967 to 1970.

I last saw Frank three years ago at his home in Cambridge, Massachusetts. Even at 92, he was intensely interested in my science, just as he had been when I was a graduate student. My plan was to give a private seminar about my most recent work, but I didn't get far before he was reminiscing about his career and how science had changed. As he observed in my work, X-ray crystallography is now used routinely to obtain enzyme structures, providing once unimaginable information for determining their modes of action. It was humbling to recall that his pioneering work on alcohol dehydrogenase was achieved without even the benefit of NMR. But although experimental tools have changed, the intellectual guidelines established by Westheimer for understanding the chemical basis of biology will endure for ever.

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