Obituary

Jacques H. van Boom (1937–2004)

Jacques van Boom, who died on 31 July, is best known for his seminal work in synthesizing strings of nucleic acids of defined sequence. Such oligonucleotide sequences are now made and delivered with a 24-hour turnaround time, but it wasn't always so. In the late 1970s, workable methods for producing them were few and far between, especially for the large quantities required for structural studies. Much of the revolution in biology that stems from techniques such as the polymerase chain reaction, or site-directed mutagenesis, would have been impossible without easy access to oligonucleotides of defined sequence.

More generally, much of the chemistry that has found its way into applications now considered routine in the life sciences has its roots in the pioneering work of chemists such as van Boom — the synthesis not only of nucleic acids, the building-blocks of DNA, but of chains of peptides and sugars (oligo- and polysaccharides) as well.

Van Boom was born in 1937 in Simpelveld, in the Netherlands. He studied chemistry at Utrecht University, obtaining his PhD there in 1968. Following postdoctoral training in the laboratories of Lord Todd and C. B. Reese at the University of Cambridge, he turned his attention to the development of ways of synthesizing nucleic acids. Following a move to Leiden University, where he became a professor in 1975, he developed a new series of phosphorylation techniques as essential intermediates for the synthesis of oligonucleotides. The most prominent of these approaches was his modification of the so-called phosphotriester method; although van Boom's methods have been superseded by phosphoroamidite chemistry, they did allow the synthesis of pure oligonucleotides on solid supports, and in automated fashion in amounts that could be studied structurally.

One such oligonucleotide, CGCGCG, a self-complementary hexamer, became the subject of a highly successful collaboration, begun in the late 1970s, between van Boom and Alex Rich, at the Massachusetts Institute of Technology. With milligram quantities of the pure oligonucleotide to hand, Rich and his colleagues succeeded in obtaining crystals that diffracted to 0.9 Å, yielding a structure of the oligonucleotides at atomic resolution.

Here it needs to be remembered that although the famous Watson–Crick model

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of DNA, based on fibre diffraction patterns obtained by Rosalind Franklin and Maurice Wilkins, was consistent with the data then available, it lacked the atomic resolution of the single crystal analysed by Rich and van Boom. As Rich tells the story, even though every atom in the six-base-pair structure was visible, the structure itself could not be modelled as the typical B (right-handed helix) form of DNA, but rather surprisingly revealed itself as a left-handed helix. Francis Crick, apprised of this fact by Rich ("Francis, we have the structure, and it's a left-handed helix!"), was nonplussed — until Rich pointed out that van Boom's oligonucleotide assumed a conformation previously inferred from circular-dichroism data obtained for DNA in high salt concentrations, as an alternative ('Z' form) to the more common B form of DNA seen with low salt.

Refining his synthetic methods to include modified nucleotides, van Boom, with Sidney Hecht, went on to work out the mode of action of the DNA-targeting antibiotic bleomycin.

Van Boom's more recent work extended to the synthesis of peptide–nucleotide molecules, which (with Eckard Wimmer) in 1998 were used successfully to unravel the replication mechanism of poliovirus. This required the synthesis of homogeneous peptides with uridyl groups attached, and necessitated a successful joining-at-the-hip of peptide and nucleic-acid chemistry.

The automated, solid-phase synthesis of oligosaccharides of predetermined length and structure has, however, been a much tougher nut to crack. Nonetheless, an early highlight in the area of glycobiology was the development of a synthetic vaccine against *Haemophilus influenzae* type b, which causes pneumonia and meningitis. A synthetic conjugate vaccine against this bacterium, produced essentially by the route reported by van Boom, is effective and in use.

In the early 1990s, van Boom worked out a set of activator systems that turn sugars containing sulphur (thioglycosides) into effective donors for oligosaccharide assembly because of their intrinsic stability under many synthetic conditions. With the development of suitable promoter systems, thioglycosides are now used as donor or acceptor in oligosaccharide synthesis and have facilitated the synthesis of many oligosaccharides and conjugates between sugars and other molecules, both in solution and on solid supports. Van Boom's description of the thioglycoside method, published in *Tetrahedron Letters* in 1990, is one of the most cited papers in modern carbohydrate chemistry. Applications include the industrial-scale fabrication of heparin analogues to control blood clotting.

The Netherlands is a small country with a small scientific community, and van Boom's passion for science was at times mistaken for brusqueness and an unwillingness to get involved. Quite simply, however, he had an aversion to any activity that did not involve science itself. He distilled most of the commonly used solvents himself, an activity that not only saved his students' time and the lab money, but also provided him with a ready excuse to leave meetings he considered useless. His preferred mode of transport, a moped, sometimes used even in the lab corridors, similarly allowed him to claim mechanical breakdown as a means of avoiding unproductive meetings. His brutal honesty in scientific matters was paired with a *joie de vivre* more typical of the Burgundy-oriented southern Netherlands than the damp and puritanic north.

A heavy smoker, he died of lung cancer. He leaves behind his wife Liesbeth, a daughter and two grandchildren.

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