

## Daniel S. Kemp (1936–2020): A Pioneer of Bioorganic Chemistry

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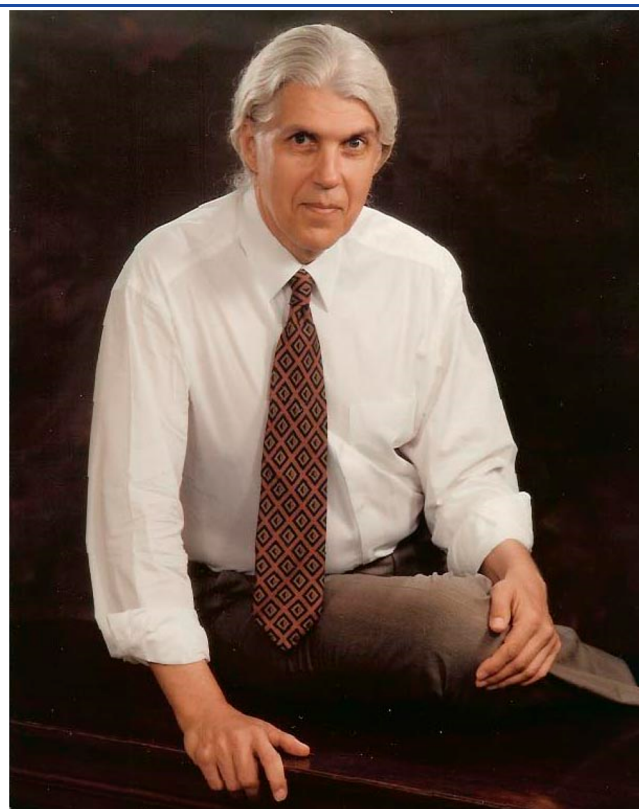
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A hallmark of chemical biology is its ability to address biological challenges with chemical approaches derived from basic principles. Dan Kemp made seminal contributions toward this end. His research on the design and synthesis of molecular scaffolds laid an inspirational cornerstone for contemporary chemical biology.

Daniel Schaeffer Kemp was born in Portland, Oregon and raised in Missoula, Montana. He returned to Portland to study chemistry at Reed College, where he performed research with Arthur F. Scott on the reactivity of divalent chromium. He was a National Science Foundation graduate fellow at Harvard University under the supervision of R. B. Woodward, doing research on the reactivity of the *N*-ethylbenzisoaxazolium cation.<sup>1,2</sup> Following election to the Harvard Society of Fellows, Kemp joined the faculty of the Department of Chemistry at MIT. He was on the faculty there for over 40 years, supervising the doctoral research of 55 graduate students and mentoring dozens of postdoctorates and undergraduate students. Alumni from his laboratory have become renowned leaders in academia and industry. Here, we recount the impact of his research related to peptides and proteins.

Modern methods of protein synthesis rely on the ligation of synthetic peptides. The intellectual underpinnings for this field were spawned in the Kemp laboratory. The basis was established in 1975, when Kemp showed that a carbinolamine could “capture” a proximal ester.<sup>3,4</sup> Throughout the 1980s, this concept evolved in the Kemp laboratory based on a key revelation: “Of the functional groups that appear in peptides, the thiol function of cysteine offers the greatest potential for meeting the...capture requirements.”<sup>5</sup> Kemp’s “prior thiol capture” method employed 4-hydroxy-6-mercaptodibenzofuran to enforce proximity between coupling partners (Figure 1). The strategy uses a thiol–disulfide exchange reaction in a capture step prior to an O→N acyl transfer reaction. Reduction of the disulfide bond yields the peptide product. Kemp and his research group demonstrated the utility of prior thiol capture in a variety of topical contexts.<sup>6,7</sup>

With his prior thiol capture strategy, Kemp was the first to demonstrate the chemoselective ligation of unprotected peptide fragments. In addition, he was the first to use a transient covalent bond to facilitate the ligation of peptides. These two concepts are central to modern methods of protein synthesis.

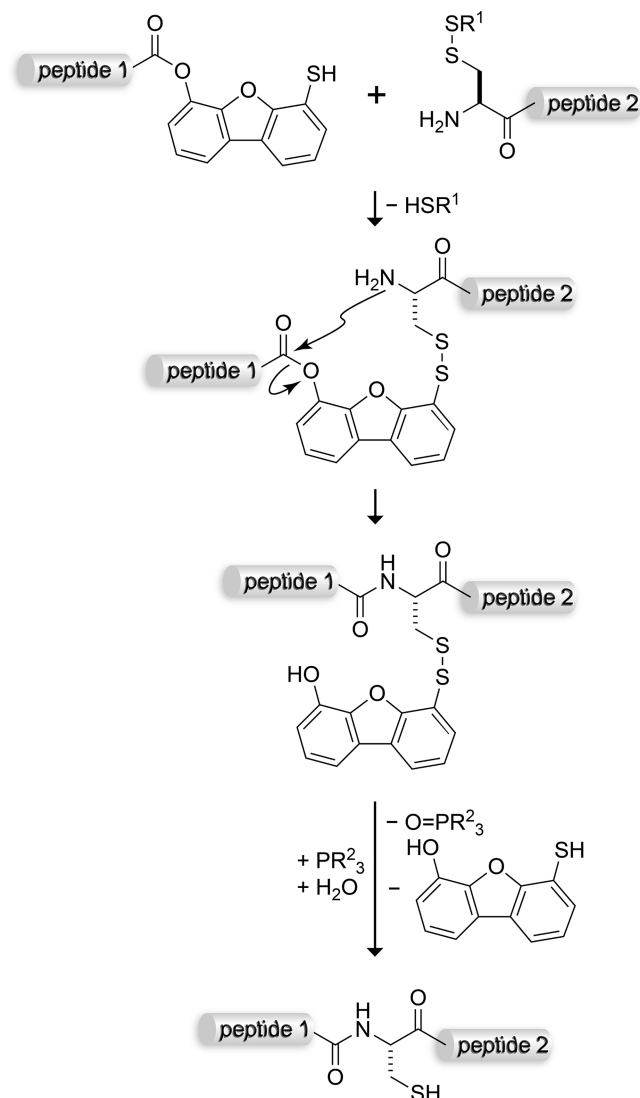


Daniel S. Kemp (1936–2020)

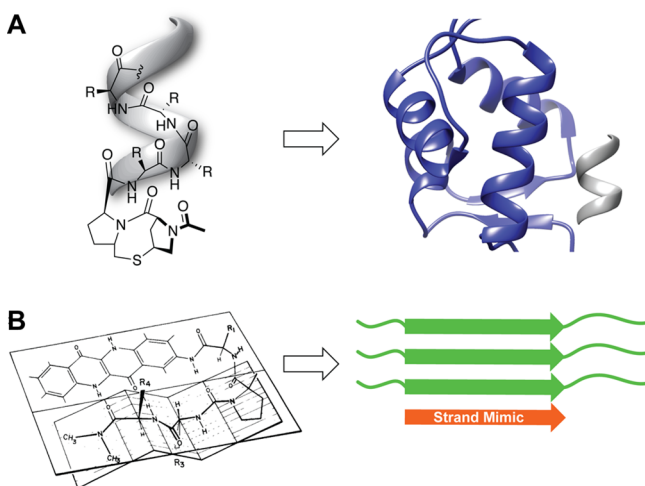
In the 1990s, Kemp’s work on peptides transitioned from their synthesis to their conformational control.<sup>8</sup> In groundbreaking work, he pioneered the use of scaffolds to stabilize the most abundant secondary structural elements in proteins: the  $\alpha$ -helix and the  $\beta$ -sheet. Early on, Kemp recognized that the intrinsic constraints of proline could be useful in an  $\alpha$ -helix template. Guided by meticulous models, he discovered that a properly placed thioether bridge constrains vicinal proline residues in an ideal conformation for helix nucleation (Figure 2A). His scaffold enabled him to estimate helix-propensity

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**Figure 1.** Kemp's prior thiol capture strategy for peptide ligation.



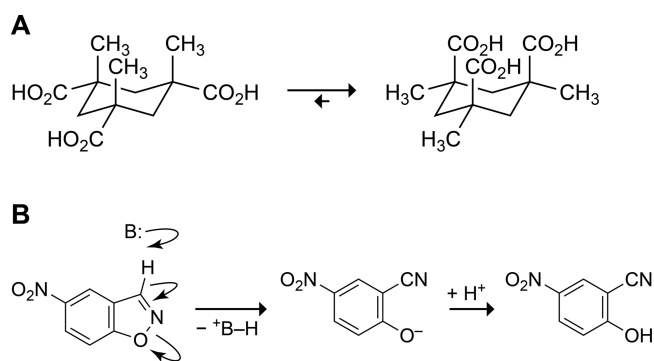
**Figure 2.** Kemp's synthetic scaffolds for stabilizing  $\alpha$ -helices (A) and  $\beta$ -sheets (B).

values for pendant amino acid residues.<sup>9</sup> Although other (e.g., protein-based) models for quantifying helical propensity have been described, Kemp's work is rarefied in its not only

providing data in isolated peptides (where protein packing does not influence helix stability) but also and more importantly employing a prenucleated helix, which allows for a measure of helix propagation apart from helix initiation. These early synthetic strategies provided the conceptual framework for helices constrained by either hydrogen-bond surrogates or “staples,” which have become a mainstay for antagonizing protein–protein interactions.

Likewise, Kemp developed a scaffold for a  $\beta$ -sheet. Again, he relied on models, here that would enable him to enforce the geometry of hydrogen bonding between  $\beta$ -strands. He identified 2,8-diaminoepindolidione as an optimal template (Figure 2B).<sup>10</sup> The contours of his design can be seen in contemporary efforts to inhibit amyloid aggregation with preorganized  $\beta$ -strand mimics.

Finally, we note that the Kemp name is embedded within the vernacular of bioorganic chemistry. Foremost is “Kemp’s triacid” (Figure 3A).<sup>11</sup> The equilibrium between its two chair



**Figure 3.** An eponymous compound and reaction. (A) Kemp's triacid. (B) The Kemp elimination.

conformations provides educators with exemplary lessons on the steric strain of 1,3-diaxial interactions and A values ( $\text{CH}_3 > \text{CO}_2\text{H}$ ). The enforced intimacy of its 1,3,5-*cis*-carboxy groups has enabled enlightening studies on the energetics of hydrogen bonding and the contribution of proximity to chemical reactivity. By elaboration of its triaxial carboxy groups, Kemp's triacid has served as the linchpin for novel supramolecular structures and a template for the collagen triple helix and other trimeric architectures. Moreover, the "Kemp elimination",<sup>12,13</sup> in which a benzisoxazole<sup>1,2</sup> isomerizes to a salicylonitrile (Figure 3B), is an oft-used model reaction for the development of novel enzymic and other catalysts.

The scientific achievements of Dan Kemp led to his receipt of an Arthur C. Cope Scholar Award and the Ralph F. Hirschmann Award in Peptide Chemistry from the American Chemical Society, along with many other accolades. He was also a masterful teacher of chemistry and was celebrated for his captivating lectures in both undergraduate and graduate classrooms. Together with Frank Vellaccio, he wrote an influential textbook and associated workbook that modernized organic chemistry pedagogy and included prescient chapters on “Amino Acids, Proteins, and Nucleotides” and “Sugars and Oligosaccharides.”<sup>14</sup>

In May 2020, Dan Kemp became a victim of the COVID-19 pandemic. As both the founder of the fields of templated peptide ligation and nucleated helices and sheets and an inspirational mentor and educator, he left an extraordinary legacy to chemical biology.

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