

The Pattison Lecturer for 2002-2003

Prof. Richard V. Wolfenden

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University of North Carolina at Chapel Hill

Richard Wolfenden received a bachelor's degree in chemistry from Princeton University in 1956. He received both bachelor's (1958) and master's (1960) degrees in animal physiology from Oxford University and his doctorate from Rockefeller University in 1964. He joined the UNC faculty in 1970 and was appointed Professor of Biochemistry in 1973. Since 1983, he has been the Alumni Distinguished Professor of Biochemistry. Professor Wolfenden currently serves as chairman of the biological division of the American Chemical Society. He has received much recognition for his contributions to research including the NIH Research Career Development Award (1971-1976); Fellow of the American Association for the Advancement of Science (1983); Member, Editorial Board, Bioorganic Chemistry (1983-); North Carolina Distinguished Chemist Award, ACS (1990); Member, Editorial Board, Bioorganic and Medicinal Chemistry and Bioorganic and Medicinal Chemistry Letters (1989-); an elected Fellow of American Academy of Arts and Sciences (2002). Most recently, his distinguished and continuing original research achievements have been recognized by election as a Member of National Academy of Sciences (2002). Wolfenden's work on enzyme mechanisms and water affinities of biological compounds is considered a major influence in these research areas. His research has also influenced rational drug design based on transition state mimics. Findings from his laboratory helped spur development of ACE inhibitor drugs, a widely used type of medication for hypertension. Recent studies have focused on the catalytic power of enzymes, how they accelerate the rates of biochemical reactions by factors in excess of a quadrillion (10 to the 15th power). He has pioneered the technically challenging measurement of rates of uncatalyzed analogs of enzyme catalyzed reactions.



From June 2nd to June 4th, Professor Wolfenden will present three lectures.

[For more information click here.](#)

Professor Wolfenden will present three lectures during his visit to UWO.

***** All lectures will take place at 3:00 p.m. in the Biological and Geological Building *****

(B & G Room 22)

1. Enzymes as Targets for Drug Design

Monday, June 2, 3:00 p.m., B & G 22

An enzyme, or any other catalyst, lowers the activation barrier that limits the rate of reaction. That can only be accomplished to the extent that the enzyme binds the altered substrate (S^\ddagger), in the transition state for its transformation, more tightly than it binds the substrate (S) in its ground state. During that moment, lasting perhaps 10-13 sec, the "grip" of the enzyme on the substrate tightens by a factor that equals or exceeds the factor by which the enzyme enhances the rate of reaction. This picture of catalysis focuses attention on a structure, rather than a process, and leads to a testable prediction. A stable compound that resembles S^\ddagger should be a potent inhibitor, with an affinity surpassing that of the substrate by a very large factor. Nearly all the structural features of S are usually present in S^\ddagger , and the differences between them seem to be so few in number that an enzyme's ability to distinguish between these structures, in terms of binding affinity, seems doubly startling. Our laboratory has been trying to work out the implications of this idea for probing enzyme mechanisms, and for designing enzyme antagonists as potential drugs. Some possible answers will be illustrated with the results of recent experiments involving mutation of the active sites of cytidine deaminase and OMP decarboxylase, and of their substrates and inhibitors.

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2. Enzymes as Time Machines

Tuesday, June 3, 3:00 p.m., B & G 22

The slow progress of biological reactions in the absence of catalysts offers a standard by which to judge the catalytic power of existing enzymes, and their potential susceptibility to inhibition by ideal transition state analogue inhibitors. By comparing different enzymes with respect to the rate enhancements that they produce, it should be possible to identify those enzymes that offer the most sensitive targets for inhibitor design. With the exception of a few relatively fast reactions such as the hydration of CO_2 , most biological reactions proceed so slowly that their rates have often been regarded as beyond the possibility of measurement in the absence of enzymes, even using Arrhenius plots. Indeed, many spontaneous reactions would be far too slow to follow at temperatures below the critical point of water if they doubled in rate as the temperature increases by 10°C . That property, first described by Harcourt in 1870, has since been imputed to other reactions in aqueous solution by most textbooks that have anything to say about the matter. Recent experiments have shown that this generalization is very far from the truth, and that in the absence of enzymes, some uncatalyzed reactions are slow even on a cosmological time scale.

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3. Conflicting Structural Requirements of Substrate Access and Transition State Affinity

Wednesday, June 4, 3:00 p.m., B & G 22

The affinity of an enzyme for the altered substrate in the transition state, and its ability to distinguish between S and S^\ddagger , presumably depend on structural complementarity between the host and its guest. Upon first glance, one might guess that optimal affinity would be observed if the enzyme's active site, in its native or most stable form, were rigidly designed to form a perfectly-fitting template for S^\ddagger . It was therefore startling when X-ray diffraction from one of the first transition state analogue complexes revealed a striking change in the enzyme's crystal structure. If that behavior were general, then it might be a mistake to attempt to design an analog to fit the native, or open, configuration of the enzyme. Alternation of an enzyme between open and closed configurations might allow rapid substrate access to be reconciled with tight binding in the transition state, if the enzyme were able to move easily between these structural extremes, as in the opening and closing of a first baseman's glove. Recent evidence bearing on that possibility has come from an unexpected source: mass spectrometry.

Refreshments served before talks

For more information contact: [Robert Hudson](#) (519-661-2111 ext. 86349)

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