

This Week's Citation Classic®

Snell E E. Chemical structure in relation to biological activities of vitamin B₆.
Vitam. Horm. 16:77-125, 1958.

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After a brief historical résumé, this review summarizes the relation of chemical structure to the catalytic activity of pyridoxal in nonenzymatic systems and relates these results to the catalytic activity of pyridoxal 5'-phosphate in enzymatic reactions. It then presents a general mechanism for such reactions and an interpretation of the action of inhibitors related to vitamin B₆. [The SCI® indicates that this paper has been cited in more than 325 publications.]

Structure and Function of Vitamin B₆

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During studies leading to the discovery that vitamin B₆ was a complex and that its active forms for lactic acid bacteria were pyridoxal and pyridoxamine,¹ I observed reversible nonenzymatic transamination between pyridoxal and amino acids² and suggested, correctly as it turned out, a coenzymatic role for the vitamin in enzymatic transamination.^{1,2} This result led us to study reactions of pyridoxal with other amino acids; this survey revealed an amazing (to us) correspondence between these reactions and enzymatic reactions for which coincident studies in other laboratories were showing the coenzyme pyridoxal 5'-phosphate (PLP) to be required. It appeared as though pyridoxal itself was a primitive "enzyme" whose catalytic potentialities were quantitatively enhanced and lent specificity but were not qualitatively changed by association with an apoenzyme.

We could now test pyridoxal analogues in the nonenzymatic model system and thus distinguish those structural features necessary for catalysis per se from those necessary for association with apoenzyme. These studies led us to suggest a general

mechanism³ for reactions catalyzed by pyridoxal (and, by extension, PLP) that has itself become a *Citation Classic*.

By the time I moved to Berkeley, California, in 1956, my colleagues and I had largely completed this survey. A temporary suspension of research occasioned by this move provided time to reflect further on the significance of such structure/function relationships in the model systems for both coenzymatic and vitamin activity.

This review article was the result. I suspect (with no real evidence) that one reason it has been widely quoted is that it presented our ideas concerning the mechanism of vitamin B₆ function in a somewhat less technical way than the original articles on which it was based, summarized these articles in a single location, and included a summary of the metabolic interconversions leading from various forms of vitamin B₆ to PLP. Most of the articles on the mechanism had appeared in chemical journals, and the review made these ideas conveniently available for the first time to nutritionists and other more physiologically oriented research workers. Also, I believe it provided the first reasonably complete interpretation of the relation of chemical structure of any vitamin to its enzymatic functions.

In retrospect, of course, I realize that some aspects of the topic were overinterpreted or oversimplified. For example, it would be more accurate to state that apoenzymes in the enzymatic systems provide a *functional* (and more efficient) replacement for the catalytic metal ions of the nonenzymatic model systems than to state that the apoenzymes *replace* the catalytic metal ions in the model systems. On the whole, however, the main points made in the review are still valid. Unfortunately, some of the gaps in knowledge alluded to there remain unfilled even today.

1 Snell E E. The vitamin activities of "pyridoxal" and "pyridoxamine" *J. Biol. Chem.* 154:313-4, 1944 (Cited 105 times since 1945)

2 ----- The vitamin B₆ group V The reversible interconversion of pyridoxal and pyridoxamine by transamination reactions. *J. Amer. Chem. Soc.* 67:194-7, 1945 (Cited 140 times.)

3 Metzler D E, Ikawa M & Snell E E. A general mechanism for vitamin B₆-catalyzed reactions. *J. Amer. Chem. Soc.* 76:648-52, 1954. (Cited 650 times) [See also Metzler D E. *Citation Classic. Current Contents/Life Sciences* 29(16):21, 21 April 1986.]

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