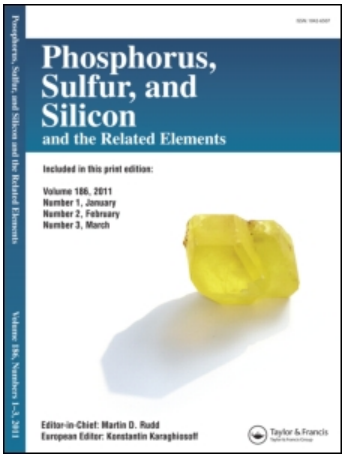

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A Hapten for the Generation of Antibody Phosphatases

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A HAPTEN FOR THE GENERATION OF ANTIBODY PHOSPHATASES

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Abstract A series of hydroxymethylene and α,β-unsaturated aminophosphinic acids was prepared, modelled on the 'exploded' transition state proposed (Herschlag [1]) for the chemical hydrolysis of phosphate monoesters. They exhibit the dual utility of being transition state analogues for the chemical hydrolysis of phosphate monoesters and having the potential for inhibition of phosphatase enzymes. (**1**) was chosen to be utilised as a hapten molecule for the generation of catalytic antibodies.

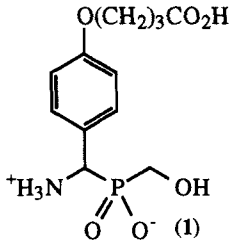
Key Words: Catalytic, Antibodies, Phosphatase, Hapten, Abzymes

PHOSPHATE MONOESTER HYDROLYSIS

A large number of abzymes has been reported capable of the cleavage of aliphatic esters. Examples of antibody phosphatases, however, are few and show rather small rate enhancements (Scanlan [2]). By examining the proposed transition state for chemical hydrolysis, it is hoped to elicit antibodies that are both prolific and specific.

Modelling the Transition State

The enzymic process occurs *via* enzyme serine phosphorylation. The chemical process, however, proceeds *via* a 'metaphosphate-like' transition state. The well-developed leaving group positive charge and the negatively charged 'metaphosphate' are mimicked in hapten molecule (**1**) by a zwitterionic amino phosphinic acid moiety. The hydroxymethylene unit serves as a model for an incoming nucleophilic water molecule. The overall hapten dimensions serve to imitate the large amount of bond breaking and small amount of bond making present in the 'exploded' transition state.



(**1**)

The synthesis of the hapten (**1**) is achieved in 7 steps from 4-hydroxybenzaldehyde. Williamson ether addition appends the linker moiety, followed by formation of the aldehyde bisacetamide with acetamide in refluxing acetic acid/acetic anhydride. Treatment with hypophosphorous acid in refluxing acetic acid affords the N-acetyl phosphonous acid, which is not isolated, but hydrolysed and protected to yield the CBZ-amino acid. Hydroxymethylation with gaseous formaldehyde /TMSCl/Et_3N and subsequent deprotection furnishes hapten (**1**) ready for conjugation to carrier protein.

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2. T. Scanlan, J.R. Prudent, P.G. Schultz, *JACS*, **113**, 9397 (1991).