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## Structural changes during the enzymic action of isopropylmalate dehydrogenase

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IPMDH is essential for leucine biosynthesis in bacteria and plants catalysing the oxidation of 3-isopropylmalate (IPM) to 2-oxo-isocaproate by NAD in the presence of  $Mn^{2+}$ . Single crystal microspectrometry has shown that in crystals of  $IPMDH/MnIPM$  and of  $IPMDH/MnNAD$  the diffusion of the other substrate (respectively NAD or IPM) causes the appearance of the NADH band. The reaction might be limited by diffusion of the substrate or by lattice forces. An active site mutant (K185A) has been produced that exhibits 0.06 % catalytic activity of the native enzyme. The possibility of obtaining a crystal of the mutant enzyme containing both bound substrates before occurring the reaction has been exploited, but resulted in a crystal with the bound reaction products. This structure (2.2 Å,  $R_{free}=23\%$ ) shows an enzyme conformation similar to the *IPMDH/MnIPMNADH complex*, and possibly to the active *IPMDH/MnIPMNAD<sup>+</sup> complex*.

We thus plan to grow crystals of the above reported complexes of the mutant enzyme in order to be able to follow the enzymic reaction upon diffusion of the omitted NAD<sup>+</sup> or Mn\*IPM into them. Simultaneous combination of X-ray diffraction and in situ spectroscopy is expected to reveal the structural changes during catalysis by IPMDH.

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