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AP endonucleases and AP lyases

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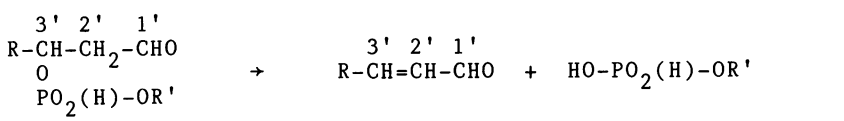
DNA repair enzymes that specifically incise at AP (apurinic and apyrimidinic) sites were discovered in the early 1970's in Escherichia coli and in mammalian cells (1,2). The major activities of this kind in E.coli are endonuclease VI (which is the same protein as exonuclease III) and endonuclease IV, and in mammalian cells a Mg^{++}-dependent AP endonuclease. Subsequent studies on the mode of action of these enzymes have shown that they catalyze the hydrolysis of the C3'-O-P bond 5' to the AP site (3,4). Following the recommendations (1984) of the Nomenclature Committee of the International Union of Biochemistry (5) these proteins belong to class 3 of the six main divisions of enzymes : "Class 3. Hydrolases. These enzymes catalyze the hydrolysis of various bonds.... While the systematic name always includes 'hydrolase', the recommended name is, in most cases, formed by the name of the substrate with the suffix -ase. It is understood that the name of the substrate with this suffix means a hydrolytic enzyme". Further, AP endonucleases belong to subclass 3.1 as "acting on ester bonds" and have been classified (1984) as 3.1.25.2, that is the second type of enzymes listed within group 3.1.25 (Site specific endodeoxyribonucleases : specific for altered bases).

Studies on the incision reaction catalyzed by various enzymes at AP sites in DNA established that cleavage could occur either at the 3' or at the 5' side of the base-free residue, and these activities were subsequently called "class I" and "class II" AP endonucleases (6). However, detailed investigations of the mechanism of incision by several enzymes acting on the 3' side of the lesion established that such a cleavage invariably occurs by β-elimination and not by hydrolysis, with the generation of an unsaturated aldehyde (7,8,9 and several papers under press). The reaction is :



Consequently it would be more accurate to classify such enzymes as lyases ("Class 4. Lyases are enzymes cleaving C-C, C-O, C-N and other bonds by other means than by hydrolysis or oxidation. They differ from other enzymes in that two substrates are involved in one reaction direction, but only one in the other direction. When acting on the single substrate, a molecule is eliminated leaving an unsaturated residue. The systematic name is formed according to 'substrate group-lyase'"). More precisely, these β-elimination catalysts belong to subclass 4.2 ("Carbon-oxygen lyases. These enzymes catalyse the breakage of carbon-oxygen bond leading to unsaturated products") and should be presently placed in group 4.2.99 ("Other carbon-oxygen lyases"). The systematic name should be : AP site-DNA 5'-phosphomonoester-lyase (7); to abbreviate, we propose the name "AP lyase" (4.2.99.X) instead of the wrong appellation "AP endonuclease, class I" for such an activity. This is in analogy with the DNA photoreactivating enzyme, which was renamed deoxyribodipyrimidine photo-lyase (E.C. 4.1.99.3) when the mechanism of cleavage of pyrimidin dimers became better understood.

A complication in the present case is that all known bacterial AP lyases, and some at least of the mammalian ones, also act as DNA glycosylases and already occur in class 3.2.2 ("Hydrolysing N-glycosyl compounds"). These enzymes include E.coli pyrimidine hydrate-DNA glycosylase (also called endonuclease III), the M.luteus and phage T4 pyrimidin dimer-DNA glycosylases (also called UV endonucleases) and the formamidopyrimidine-DNA glycosylase. In these cases, we propose to use expressions such as "the AP lyase activity of the pyrimidin dimer-DNA glycosylase". It is noteworthy that several DNA glycosylases, such as uracil-DNA glycosylase and 3-methyladenine-DNA glycosylase, do not have any detectable AP lyase activity.

The β-elimination reaction that breaks the C3'-O-P bond 3' to an AP site can be followed by a δ-elimination reaction that breaks the C5'-O-P bond 5' to the AP site, with the release of an unsaturated derivative of the base-free sugar and the generation of a gap flanked by 3'-phosphate and 5'-phosphate ends (9 and other results in the press). The δ-elimination is a second β-elimination reaction (10), so the enzymes, like the formamidopyrimidine-DNA glycosylase, that catalyze a βδ-elimination reaction can also be called AP lyases.

In conclusion, the term "AP endonuclease" is sufficient for the enzymes that hydrolyse the C3'-O-P bond 5' to AP sites and there is presently no reason to use more complicated names such as "5' AP endonucleases" or "AP endonucleases, class II". On the other hand, the term "AP lyase" must replace the faulty names "3' AP endonucleases" or "endonucleases, class I". For partly purified, insufficiently characterized enzyme preparations that might act by either hydrolysis or β-elimination, non-committal terms such as "nicking activity at AP sites" would be preferable to the potential misnomer AP endonuclease for a β-elimination catalyst.

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References :

1.- Verly,W.G. and Paquette,Y. (1972); Can.J.Biochem., 50, 217-224.
2.- Verly,W.G. and Paquette,Y. (1973); Can.J.Biochem., 51, 1003-1009.
3.- Gossard,F. and Verly,W.G. (1976); Fed.Proc., 35, 1589 (abs 1179).
4.- Clements,J.E., Rogers,S.G. and Weiss,B. (1978); J.Biol.Chem., 253, 2990-2999.
5.- "Enzyme Nomenclature" (1984), ed E.C. Webb, Academic Press, pp. 1-646.
6.- Mosbaugh,D.W. and Linn,S. (1980); J.Biol.Chem., 255, 11743-11752.
7.- Bailly,V. and Verly,W.G. (1987); Bioch.J., 242, 565-572.
8.- Manoharan,M., Mazumder,A., Ransom,S.C., Gerlt,J.A. and Bolton,P.H. (1988); J.Am.Chem.Soc., 110, 2690-2691.
9.- Bailly,V. and Verly,W.G. (1988); Nucleic Acids Res., 20, 9489-9496.
10.- Grossman,L. and Grafstrom,R. (1982); Biochimie, 64, 577-580.