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A SUGGESTION TO THE PPL ACTIVE SITE MODEL DILEMMA

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Abstract: A PPL active site model with a new explanation of the nature of the hydrophobic and hydrophilic substituents of the chiral centre predicted of the PPL-mediated hydrolysis products is discussed using several examples given by the literature data, and those obtained in our research. A comparison with other PPL active site models built recently is given as well.

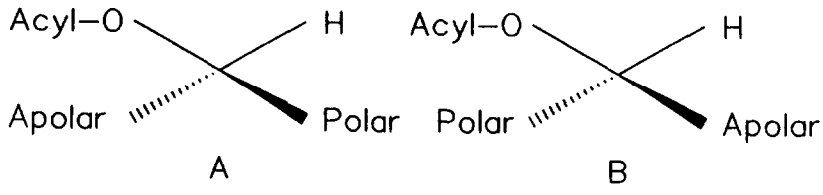
Recently two papers dealing with the porcine pancreatic lipase (PPL) active site model were published by Ehrler and Seebach[1] and Hultin and Jones.[2] Even if a large number of literature data were reviewed, neither of the models was fully successful in predicting of the stereochemistry of the favoured expected products of the PPL-mediated hydrolysis of the acetates of primary and secondary alcohols. The dilemma exists because both models mentioned are enantiomeric.[1,2]

The aim of this paper is to help in elucidating of the problem mentioned above without questioning the correctness of the models built earlier.[1,2] Our approach has been based on the modified models **A** and **B** (see **Figure 1**) in order to compare them with each other, and to compare them with the models built earlier[1,2] in predicting of the absolute configuration of the products expected. The explanation of the nature of the respective substituents located on the chiral centre studied is different from that of Hultin and Jones,[2] but closer to that mentioned by Ehrler and Seebach.[1]

The models **A** and **B** are based on an assumption that both the hydrophility and the hydrophobicity of the "polar" and "apolar" moieties in **Figure 1** are

relative conceptions, which should be extra determined for any structure studied. It seems that the following findings might help in predicting the absolute configuration of the hydrolysis products to be in correspondance with either model **A** or **B** (**Figure 1**):

a) The larger is a distance of the "hydrophilic" moiety from the chiral centre studied, the smaller is its effect in the sense of its influence on the "hydrophility" of the "polar" site;
b) An anticipated priority of the "hydrophilic" moiety located in the immediate neighborhood to the chiral centre;
c) An anticipated influence of the space orientation of non-participating substituents on final "hydrophility" or "hydrophobicity" of the respective "polar" and "apolar" substituents.



A PPL Active Site Model: The polar-site prefers moieties more polar in comparison with the apolar-site, but the findings a) to c) mentioned in the text should be respected. This means that the polar-site need not be the part of the molecule bearing the most polar moiety present in it, but the part of the molecule which is in agreement with the findings a) to c) mentioned in the text in the best way. The apolar-site prefers less polar moieties, the meaning of which can be explained on the same basis as did for the polar-site. The size of both respective sites seems to be inferiorly important. The acyl-site represents the catalytic region for the PPL-mediated hydrolysis. The H-site prefers the smallest substituent possible (a hydrogen atom); small alkyl group are also accepted, however, the larger is the substituent in this site, the worse is the enantiomeric purity of the product obtained.

Figure 1

A prediction of the absolute configuration of the products was studied using both enantiomeric models **A** and **B** (see **Figure 1**). **Table 1** shows the results of both alternative predictions in comparison with those made by means of the original Ehrler-Seebach[1] and Hultin-Jones[2] models. The model A was successful in all cases studied except of those mentioned under (a),

Table 1: A Comparison of the Results Obtained with All Respective Models

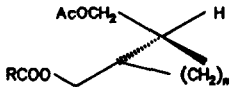
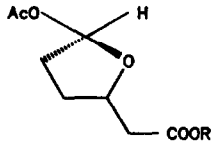
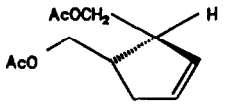
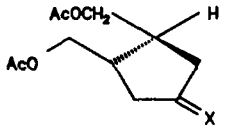
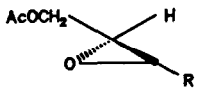
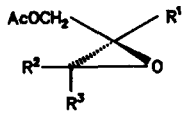
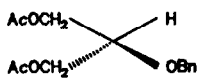
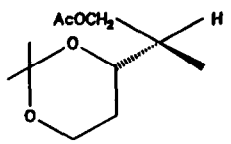
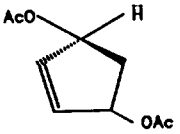
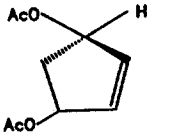
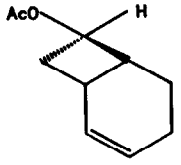
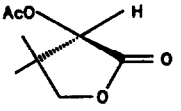
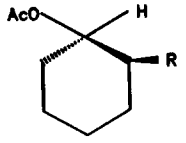
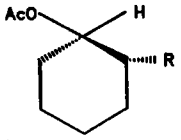
No.	Acetate[a]	Refs.	E-S model	H-J model	Model A	Model B
(a)		3	corr.[b]	incorr.[c]	incorr.	corr.
(b)		4	incorr.	incorr.	corr.	incorr.
(c)		5	corr.	incorr.	corr.	incorr.
(d)		6[d]	corr.	corr.	corr.	incorr.
(e)		7[e]	corr.	incorr.	incorr.	corr.
(f)		7[f]	incorr.	corr.	corr.	incorr.
(g)		8,9	incorr.	corr.	corr.	incorr.
(h)		10,11	corr.	incorr.	corr.	incorr.
(i)		12	incorr.	corr.	incorr.	corr.

Table 1: Continued

No.	Acetate[a]	Refs.	E-S model	H-J model	Model A	Model B
(j)		13	incorr.	incorr.	incorr.	corr.
(k)		13	corr.	incorr.	corr.	incorr.
(l)		14	corr.	incorr.	corr.	incorr.
(m)		15	incorr.	corr.	corr.	incorr.
(n)		16[g]	incorr.	incorr.	corr.	incorr.
(p)		16[g]	incorr.	incorr.	corr.	incorr.

[a] The acetate enantiomer to be hydrolyzed by the PPL, [b] correct stereochemistry predicting obtained, [c] incorrect stereochemistry predicting obtained, [d] X = O, $-O(CH_2)_2O-$, -OAc/-H, [e] R = alkyl, [f] R^1, R^2 and R^3 are alkyls or hydrogen atoms, [g] R = p-$CH_2C_6H_4OCH_3$ or p-$CH_2C_6H_4OTHP$.

(e), (i) and (j) in Table 1 (examples based on refs.[3-16]). Moreover, the structure mentioned under (i) in Table 1 was originally determined as enantiomeric.[17] In that case, the Ehrler-Seebach model, as well as the model A, would be successful. The new structure, however, determined and

published later,[12] can be predicted by the only Hultin-Jones model correctly.

Based on several examples studied, it seems that the space orientation of a non-participating substituent located on the ring (i.e. the OAc moiety in the examples (j) and (k) in **Table 1**) may be important for predicting the absolute configuration of the products with several cyclic compounds, the chiral centre of which is located in the ring (see the finding c) cited above). Predicting the absolute configuration of the chiral centre of the favoured expected products of the PPL-mediated hydrolysis of acetates of primary and secondary alcohols seems to be the most difficult task with such compounds. That is the reason, why the model **A** is not successful in predicting the correct stereochemistry with the compound under the example (j) in **Table 1**, even if it seems to do so. Regarding the findings a) and b) cited above, however, the site bearing the double bond should be considered as the more polar one of the two respective ones, even if the really more polar moiety (the remaining OAc moiety) is located in the "polar" site of the molecule when overlapped with the model **A**.

As far as several substrates synthetized in our laboratory are concerned, the absolute configurations of the PPL-mediated hydrolysis products were predicted correctly only when using the model **A** orientation (see (n) and (p) in **Table 1**).

Based on the results obtained by comparing all PPL active site models, several conclusions can be deduced:

i) The model **A** is much more successful in predicting the correct stereochemistry of the hydrolysis product than the model **B**;

ii) Neither of the models mentioned was fully successful in the above respect, but the model **A** seems to be the most satisfactory one;

iii) A successful applicability of the models suggested is limited for processing the PPL-mediated hydrolysis in aqueous media, i.e. with exluding the presence of organic co-solvents. Processing these experiments under anhydrous conditions may result in the products with different absolute configuration of the chiral centre in question which might be obtained both with different absolute configuration and with different optical purity (see for example refs.[18-22]);

iv) The size of the "polar" and "apolar" substituents seems to be of an inferior importance, otherwise the correct stereochemistry could not be predicted in several examples cited on the basis of the model **A** (see examples (h), (k), (l), (n) and (p) in **Table 1**).

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