

Computational study of the enantiomeric control of acetylation reactions by interaction with oligopeptides

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Abstract

Two systems containing a tetrapeptide in chloroform, one with and the other without a bisphenolic substrate were subjected to molecular dynamics simulations, and the number of hydrogen bonds formed between phenolic groups in the substrate and the catalyst was computed; it was found that the observed enantioselectivity contradicts the one found experimentally.

Key words: molecular dynamics; asymmetric catalysis; acetylation.

Introduction

Small polypeptides, being themselves asymmetric, may promote the emergence of asymmetries in non-chiral substrates, behaving effectively as small-scale enzymes (catalysts).

In this work, we made a computational study of the asymmetric acetylation of a bisphenolic compound (BIPH) in chloroform, which has been experimentally studied [1], assisted by a tetrapeptide (PAAS) as a catalyst in the reaction. Based on nuclear magnetic resonance (NMR) results concerning the transition state for the reaction, two mechanisms have been proposed: nucleophilic and base-assisted catalysis.

Results and Discussion

Two systems containing tetrapeptide PAAS were prepared, one with and one without the bisphenolic substrate (BIPH), both in chloroform. The systems were subjected to molecular dynamics simulations [2] using OPLS-AA [3] as the force field; the number of hydrogen bonds formed between the phenolic BIPH oxygens and PAAS was computed.

Image 1. PAAS-BIPH complex. One can clearly see the hydrogen bond between bisphenol and a sulphone in the catalyst, as well as the reactive nitrogen site in PAAS.

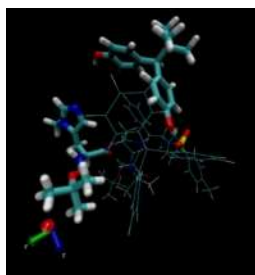


Table 1. Relative proportions (in %) of hydrogen bonds made between the substrate's oxygens (OA and OB) and some atom in PAAS (x), and between the substrate and a nitrogen (N) in the peptide associated with the nucleophilic attack in the proposed mechanisms [1].

Sim.	x---OA	x---OB	N---OA	N---OB
1	42.13	57.87	100.00	0.00
2	18.09	81.91	0.00	0.00
3	19.41	80.59	100.00	0.00
4	5.14	94.86	100.00	0.00
5	24.11	75.89	37.29	62.71
Mean	21.77	78.23	84.32	15.68

Conclusions

Analysis of the simulation results showed that there is a systematic tendency of the peptide to complex with the substrate in a way that directly contradicts the experimental results, in the context of the bifunctional hypothesis [1]; the simulations suggest that the reaction would yield mainly the opposite enantiomer than the one observed experimentally.

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