Quantum mechanical considerations on the mechanism of the P450 conversion of 11-deoxycorticosterone to Aldosterone

8151 Quantum Mechanical Considerations On The Mechanism Of The P450 Conversion Of 11-deoxycorticosterone To Aldosterone

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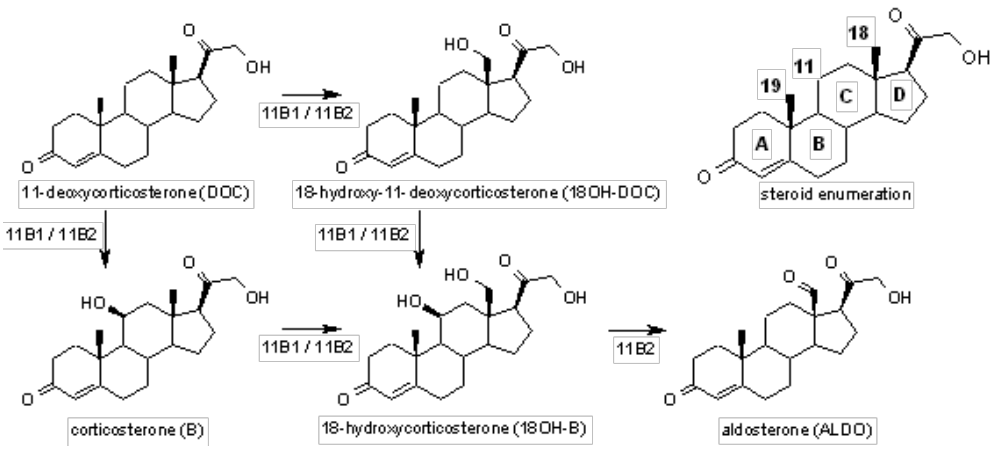
The final steps of the biosynthesis of the steroid aldosterone involve C_{11b}- and C_{18}-hydroxylations by cytochrome P450 11B1 and 11B2 (figure), and C_{18}-aldehyde production by 11B2 [1]. Generally regioselective substrate and intermediate conversions are driven by enzyme-ligand sterical and energetic factors. To evaluate in how far energetic considerations play a role in determining the sequential conversions of **DOC**, we have analysed multiple steroid conformations using Quantum Mechanics calculations. Therefore, we have conducted: (1) conformational analyses for the prediction of the optimal steroid configurations and (2) Fukui index calculations to determine the inherent reactivity of the individual carbon atoms for prediction of carbon oxidation preference. Molecule geometries were optimised using the QM package Gaussian03. Mulliken population analysis was used to determine the electron density distribution. Accurate computation of the ionic state required for the Fukui index of a nucleophilic attack, was conducted using the B3LYP functional with the 6-31+g basis set. For the lowest energy conformations of all four steroids, the Fukui index indicated that C_{19} and in some cases C_{12} were more reactive than C_{11} and C_{18}. We conclude that the 11B1 and 11B2 active site conformations must prohibit C_{12} and C_{19} interactions with the active site heme. For **DOC**, the Fukui index of C_{11} (0.088) is higher than that of C_{18} (0.043), indicating that **B** is more likely to be produced than **18OH-DOC**. The resulting conformation of **B** portrays an unfavourable C_{18} Fukui index (-0.016), but the resulting **18OH-DOC** conformation possesses a favourable C_{11} Fukui index (0.020). This can indicate two things: (1) either **B** is the most abundant product from **DOC** hydroxylation whereas **18OH-B** and aldosterone are formed via the less abundant **18OH-DOC** or (2) active site-ligand interactions result in a conformational change in the hydroxyacetyl group of **B** to allow further conversion to **18OH-B** and aldosterone. In a next step the complexity of the steroids was reduced by neglecting the A and B rings. Conformational space analyses of the simplified steroids and their calculated Fukui indices suggest that the hydroxyacetyl group of **18OH-B** requires an *anti*-periplanar conformation for conversion into aldosterone as well as an internal hydrogen bond with the C_{18} hydroxyl group.



[1] A Fisher, EC Friel, R Bernhardt, C Gomez-Sanchez, JM Connell, R Frazier, E Davies, Effects of 18-hydroxylated steroids on corticosteroid production by human aldosterone synthase and 11beta-hydroxylase, *J Clin Endocrinol Metab* (2001), 86 (9), p4326-p4329

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