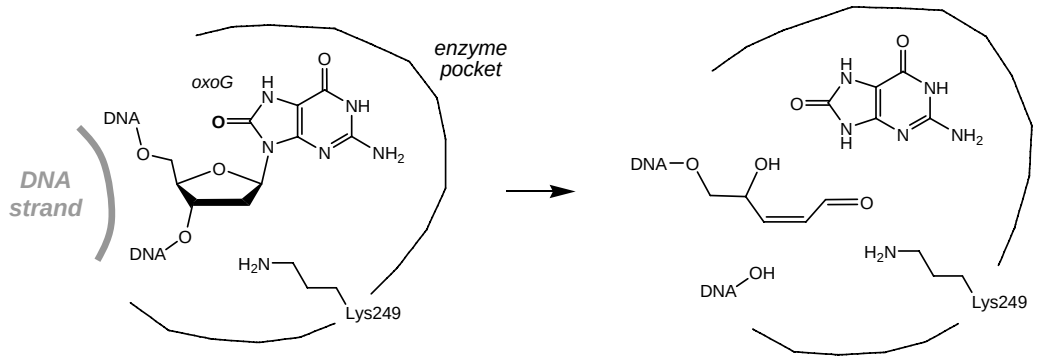
**Chemistry 4011/8011** Friday, September 15

## Workshop 2

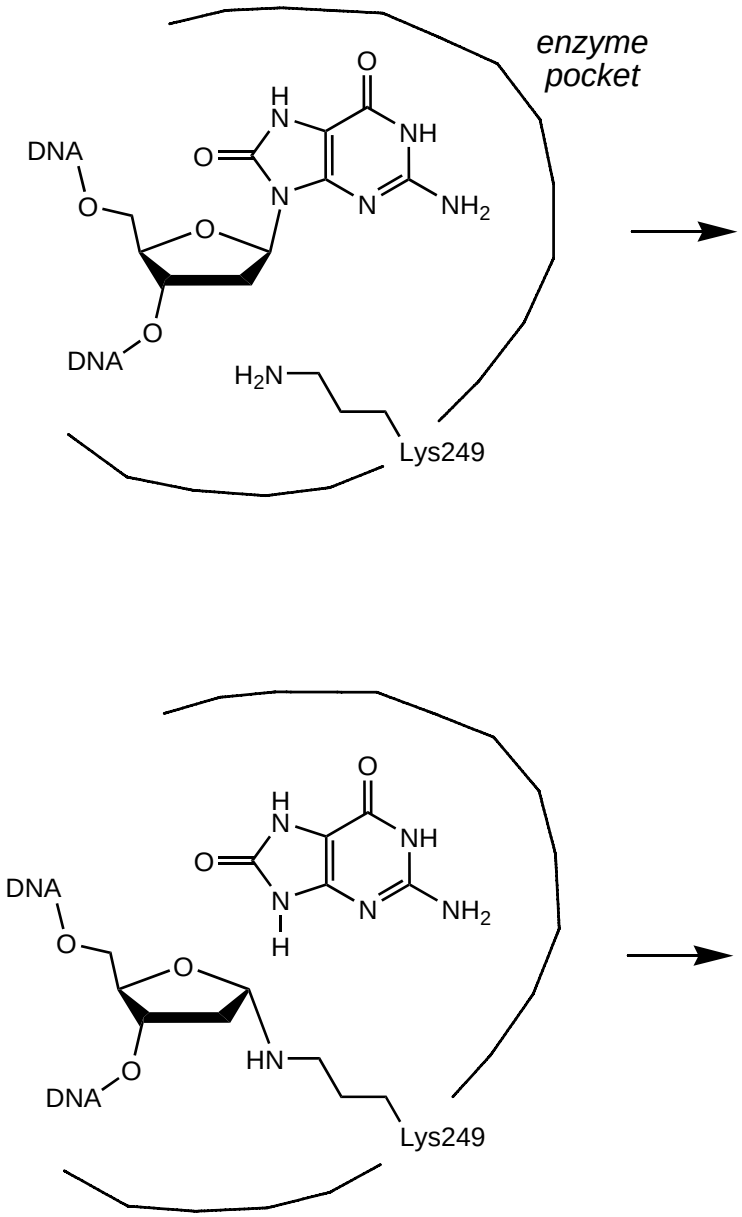
Human 8-Oxoguanine DNA glycosylase (hOGG1) is an enzyme that repairs oxidatively damaged DNA. More specifically, hOGG1 catalyzes the excision of an oxidized guanine (oxoG) base from a DNA strand, and then catalyzes cleavage of the DNA backbone. Greg Verdine and coworkers have proposed that one interesting feature of hOGG1 is that it uses the excised oxoG as a cofactor in the subsequent DNA cleavage.[1] Other than this base, the only mechanistically critical residue identified was lysine(249).




a. Some of the intermediates in the mechanism of hOGG1-catalyzed cleavage of DNA proposed by Verdine are shown on the next two pages. Using "arrow pushing", show how these intermediates are connected mechanistically. You will have to draw additional intermediates to do this. One of the reasons why the enzyme is such an effective catalyst is that it does not require multiple, diffusing species (like the generic acid "H-X" and base "B:" we used in mechanisms in class) to participate in the reaction; as a result, other than what is drawn in the catalytic pocket, the only molecule you should need is $H_2O$.

b. On page 4, the intermediates are drawn again on a blank potential energy diagram. Draw a potential energy surface that accurately reflects the relative energies of these intermediates.

[1] Fromme, J. C.; Bruner, S. D.; Yang, W.; Karplus, M.; Verdine, G. L. *Nat. Struct. Biol.* **2003**, *10*, 204-211.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NH2
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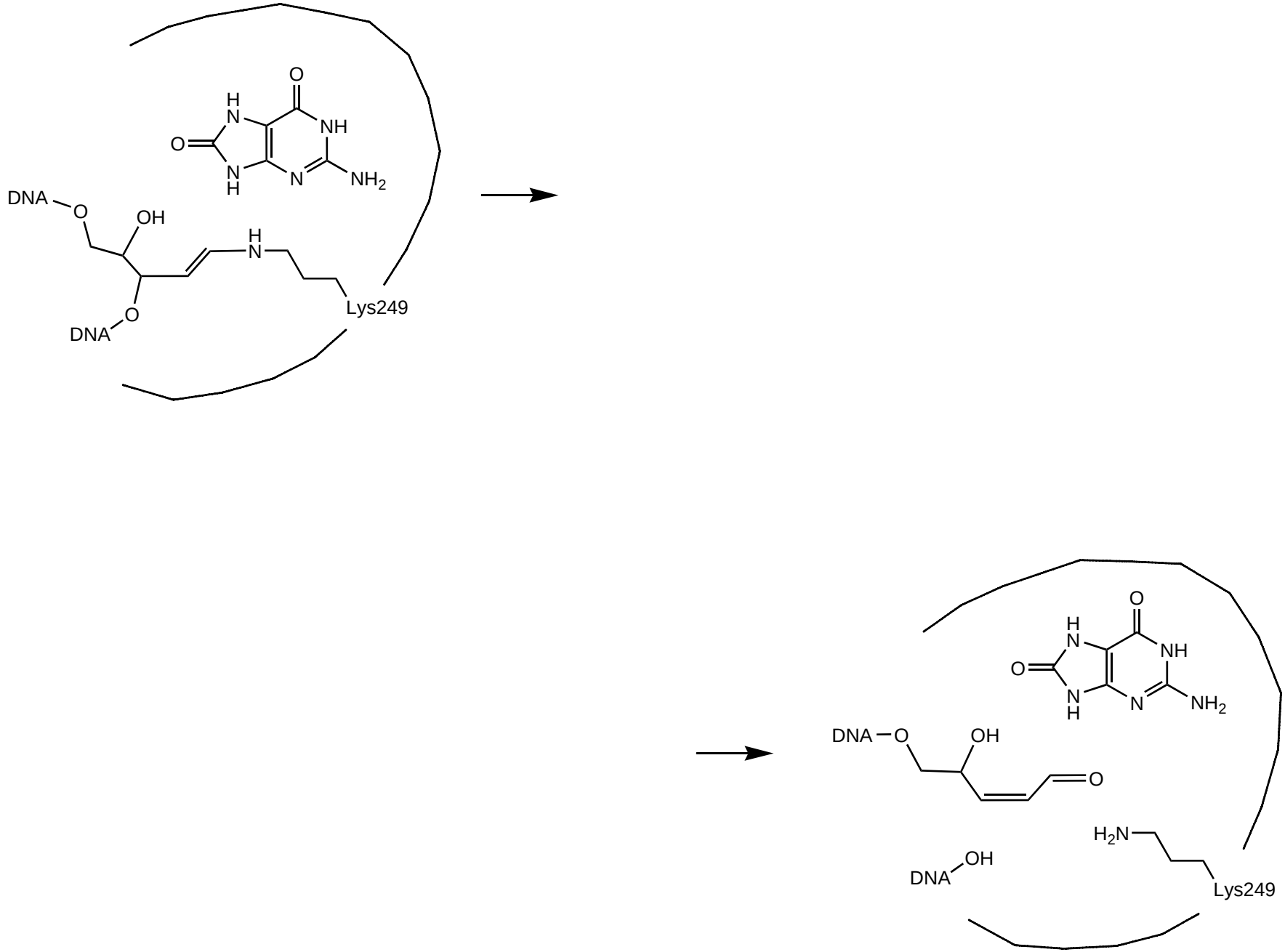
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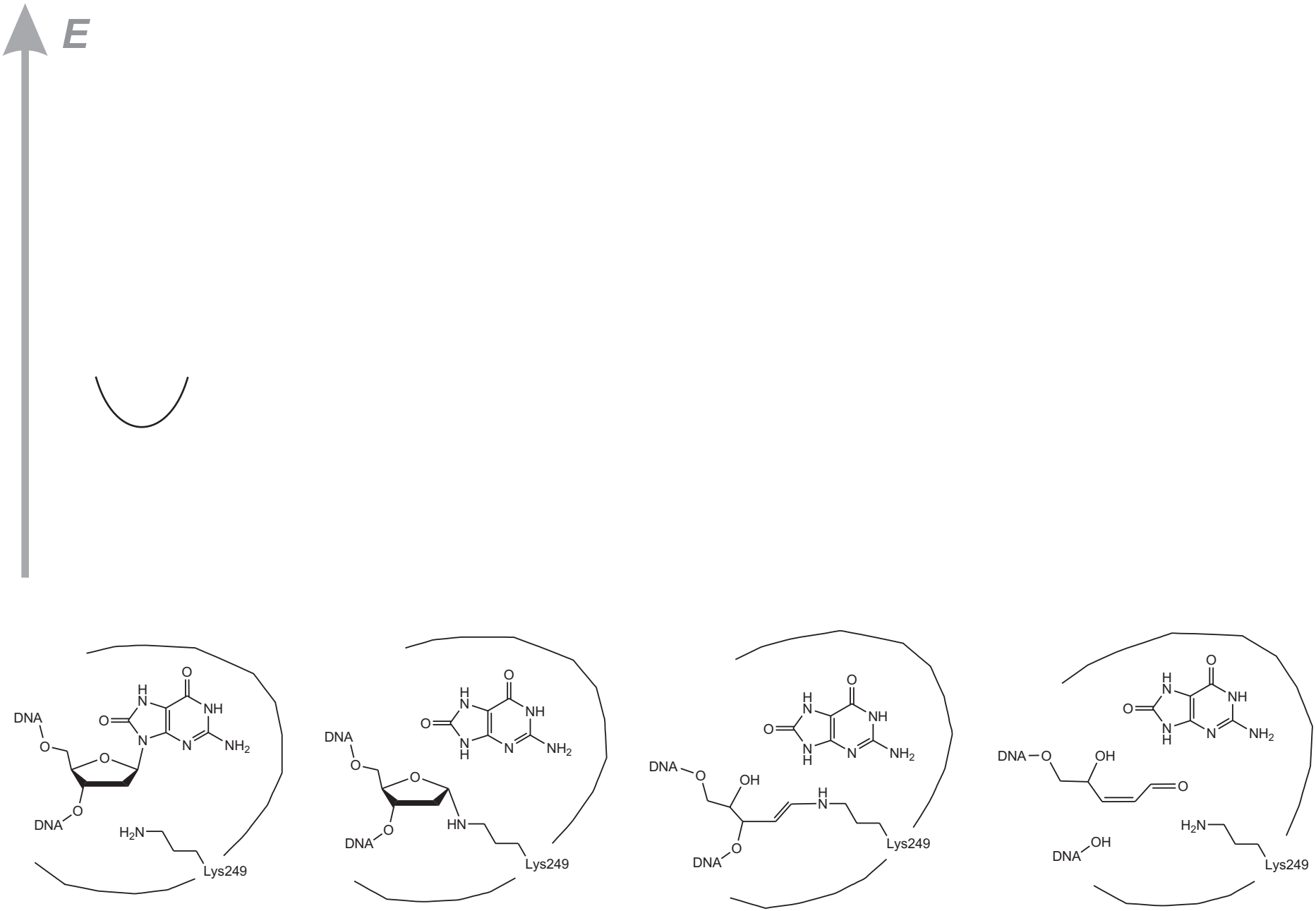
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