

New Insight into the Substituent Effects on the Hydrolytic Deamination of Saturated and Unsaturated Cytosine

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June 13, 2022

Abstract

Ab initio calculations were carried out to understand the effect of electron donating groups (EDG) and electron withdrawing groups (EWG) at the C5 position of cytosine (Cyt) and saturated cytosine (H2Cyt) of the deamination reaction. Geometries of the reactants, transition states, intermediates, and products were fully optimized at the B3LYP/6-31G(d,p) level in the gas phase as this level of theory has been found to agree very well with G3 theories. Activation energies, enthalpies, and Gibbs energies of activation along with the thermodynamic properties (ΔE , ΔH , and ΔG) of each reaction were calculated. A plot of the Gibbs energies of activation (ΔG^{++}) for C5 substituted Cyt and H2Cyt against the Hammett σ -constants reveal a good linear relationship. In general, both EDG and EWG substituents at the C5 position in Cyt results in higher ΔG^{++} and lower σ values compared to those of H2Cyt deamination reactions. C5 alkyl substituents (-H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃) increase ΔG^{++} values for Cyt, while the same substituents decrease ΔG^{++} values for H2Cyt which is likely due to steric effects. However, the Hammett σ -constants were found to decrease for both the Cyt and H2Cyt. Both ΔG^{++} and σ values decrease for the substituents Cl and Br in the reaction Cyt, while ΔG^{++} values increase and σ decrease in the reaction H2Cyt. This may be due to high polarizability of bromine which results in a greater stabilization of the transition state in the case of bromine compared to chlorine. Regardless of the substituent at C5, the positive charge on C4 is greater in the TS compared to the reactant complex for both the Cyt and H2Cyt. Moreover, as the charges on C4 in the TS increase compared to reactant, ΔG^{++} also increase for the C5 alkyl substituents (-H, -CH₃, -CH₂CH₃, -CH₂CH₂CH₃) in Cyt, while ΔG^{++} decrease in H2Cyt. In addition, analysis of the frontier MO energies for the transition state structures shows that there is a correlation between the energy of the HOMO-LUMO gap and activation energies.

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