Synthetic Analogues of Zinc Enzymes with Sulfur-Rich Active Sites

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The zinc-thiolate linkage plays an important role in the mechanisms of action of a variety of zinc proteins, as exemplified by the Ada DNA repair protein which possesses a tetrahedral $[(Cys)_4Zn^{II}]$ active site. *Tris*(2-mercaptoimidazolyl)hydroborato ligation provides a simple means to obtain zinc complexes with a sulfur rich coordination environment and $[Tm^R]ZnSR'$ derivatives [*e.g.* R' = Ph, $CH_2C(O)N(H)Ph$] thereby provide good synthetic analogues for the Ada DNA repair protein. In particular, $[Tm^{Ph}]ZnCH_2C(O)N(H)Ph$ features an intramolecular N–H···S hydrogen bond between the amide N–H group and thiolate sulfur atom, characterized by NH···S and N···S separations of 2.53 Å and 3.06 Å, respectively. $[Tm^{Ph}]ZnSCH_2C(O)N(H)Ph$ is the first example of a N–H···S hydrogen bonding interaction for a zinc complex with a tetrahedral $[ZnS_4]$ geometry. Since it has been postulated that N–H···S hydrogen bonding interactions between the thiolate sulfur and amide groups of other residues provide a mechanism to modulate the reactivity of the zinc-cysteine thiolate moiety, the reactivity of $[Tm^{Ph}]ZnSCH_2C(O)N(H)Ph$ has been examined with a view to establishing the mechanism of thiolate alkylation.

For example, the influence of the N–H···S hydrogen bond on the alkylation of $[Tm^{Ph}]ZnSCH_2C(O)N(H)Ph$ has been probed *via* measurement of the kinetic isotope effect for the isotopologues $[Tm^{Ph}]ZnSCH_2C(O)N(\mathbf{H^*})Ph$ (**H*** = H, D). Interestingly, alkylation of $[Tm^{Ph}]ZnSCH_2C(O)N(\mathbf{H^*})Ph$ is characterized by a small normal (*i.e.* $k_H/k_D > 1$) value of k_H/k_D = 1.16(1) at 0 ˚C, in marked contrast to the large *inverse* (*i.e.* $k_H/k_D < 1$) value of 0.33 reported for alkylation of $[Ph(pz^{Bu^t})Bt^{Bu^t}]ZnS[C_6H_4$-*o*-$N(\mathbf{H^*})C(O)Bu^t]$ by $PhCH_2Br$. Since an observed kinetic isotope effect corresponds to a composite of all steps up to and including the rate determining step, density functional theory calculations have been used to address how the kinetic isotope effect for methylation of $[Tm^{Ph}]ZnSCH_2C(O)N(\mathbf{H^*})Ph$ varies as a function of mechanism. However, for each of the mechanisms considered, the isotope effects at ambient temperature are predicted to be close to unity, such that the kinetic isotope effect cannot be used to provide a definitive indicator for the mechanism.