# MULTIPLE RECOGNITION BY MODIFIED CYCLODEXTRINS

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# *Abstract*

The cavity of a cyclodextrin provides a predominantly hydrophobic recognition site for guest binding. This study focuses on β-cyclodextrins which are modified at the primary rim to incorporate an additional coordination or hydrophobic recognition site.

The modified cyclodextrins $6^A$-(3-aminopropylamino)-$6^A$-deoxy-β-cyclodextrin (βCDpn) and $6^A$-(2-(*N*,*N*-bis(2-aminoethyl)amino)ethylamino)-$6^A$-deoxy-β-cyclodextrin (βCDtren) bind metal ions ($M^{2+}$ = $Ni^{2+}$, $Cu^{2+}$, $Zn^{2+}$), forming metallocyclodextrins which can complex the anions of histidine ($His^-$), phenylalanine ($Phe^-$) and tryptophan ($Trp^-$). The stability order: $[Cu(\beta CDpn)Phe]^+$ < $[Cu(\beta CDpn)Trp]^+$ < $[Cu(\beta CDpn)His]^+$, is attributed to the coordination mode of the amino acid and the size of its aromatic side chain. The greater stability of $[M(\beta CDtren)Trp]^+$, by comparison with $[M(\beta CDpn)Trp]^+$, may be attributed to steric, hydrogen bonding and dipole effects influencing cyclodextrin-$Trp^-$ interactions, and the denticity of the coordinating group affecting cyclodextrin-$M^{2+}$ interactions. The ionic radius and $d^n$ electronic configuration of $M^{2+}$ influence the stability of $[M(\beta CDtren)Trp]^+$, which follows the Irving-Williams series ($Ni^{2+}$ < $Cu^{2+}$ > $Zn^{2+}$). Guest interactions with each of the two recognition sites, reinforce each other in $[M(\beta CDtren)Trp]^+$, but not in $[Cu(\beta CDpn)His]^+$. Although $[M(\beta CDpn)]^{2+}$ demonstrates enantioselectivity for (*S*)-$Trp^-$, no enantioselectivity of $[Cu(\beta CDpn)]^{2+}$ for $His^-$, nor $[M(\beta CDtren)]^{2+}$ for $Trp^-$, is found.

The linked cyclodextrin dimers *N*,*N*'-bis-($6^A$-deoxy-$6^A$-β-cyclodextrinyl)-R, where R = urea, oxalamide, malonamide, succinamide and glutaramide ($(\beta CD)_2X$, X = Ur, Ox, Ma, Sc and Gl, respectively), form complexes with guests, possessing two aromatic binding sites. The stabilities increase as follows: $(\beta CD)_2Ma{\cdot}TNS^-$ < $(\beta CD)_2Gl{\cdot}TNS^-$ < $(\beta CD)_2Sc{\cdot}TNS^-$ < $(\beta CD)_2Ox{\cdot}TNS^-$ < $(\beta CD)_2Ur{\cdot}TNS^-$, for 6-(*p*-toluidino)naphthalene-2-sulfonate ($TNS^-$), and $(\beta CD)_2Sc{\cdot}MO^-$ < $(\beta CD)_2Ur{\cdot}MO^-$ < $(\beta CD)_2Ox{\cdot}MO^-$, for methyl orange anion ($MO^-$), and $(\beta CD)_2Sc{\cdot}TR^-$ < $(\beta CD)_2Ox{\cdot}TR^-$ < $(\beta CD)_2Ur{\cdot}TR^-$, for tropaeolin 000 no. 2 anion ($TR^-$). The overall trend in stabilities is: $(\beta CD)_2X{\cdot}TR^-$ < $(\beta CD)_2X{\cdot}TNS^-$ < $(\beta CD)_2X{\cdot}MO^-$ (X = Ur, Ox, Sc). These variations reflect differences in

binding mode and stereochemistry. The extent of cooperative binding depends on the βCD separation in $(\beta CD)_2X$, relative to the aromatic separation in the guest. These primary-primary linked cyclodextrin dimers bind $TNS^-$ more strongly than their secondary-secondary and primary-secondary analogous.

This work furthers understanding of the effects of multiple recognition sites on guest binding and selectivity.