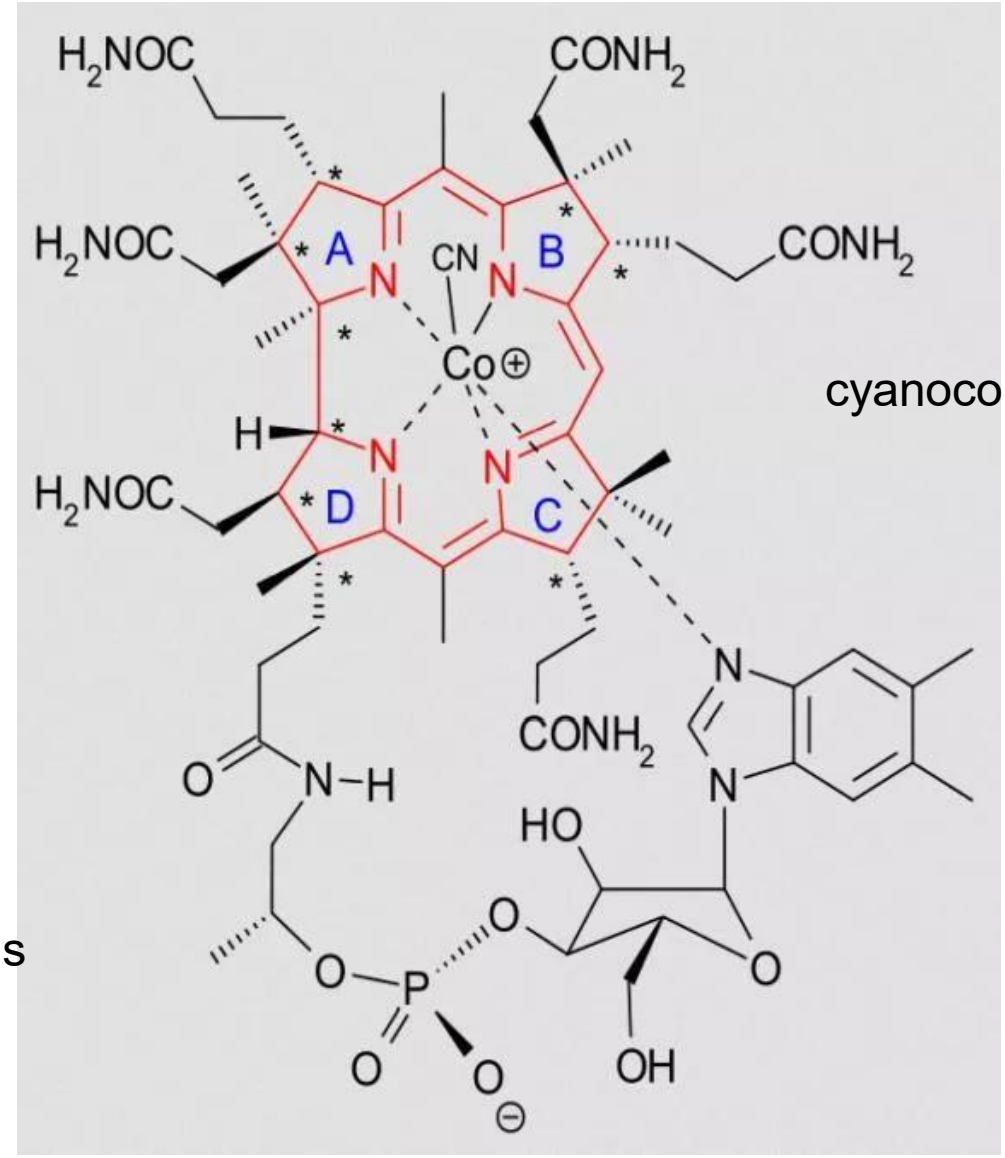
Vitamin B_{12}

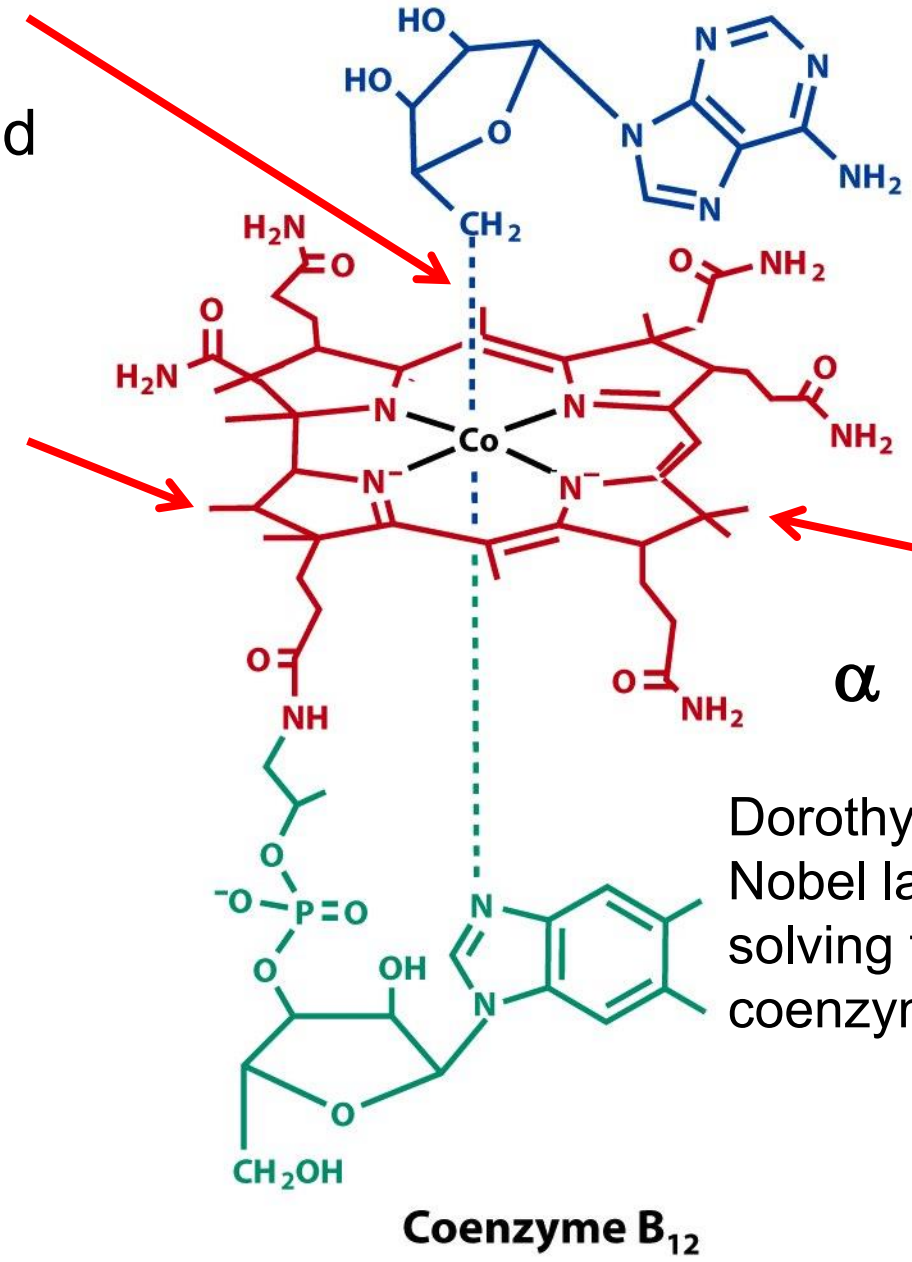


cyanocobalamin

A human body contains ca. 1 mg of Co; daily uptake 1 – 5 μg

1955

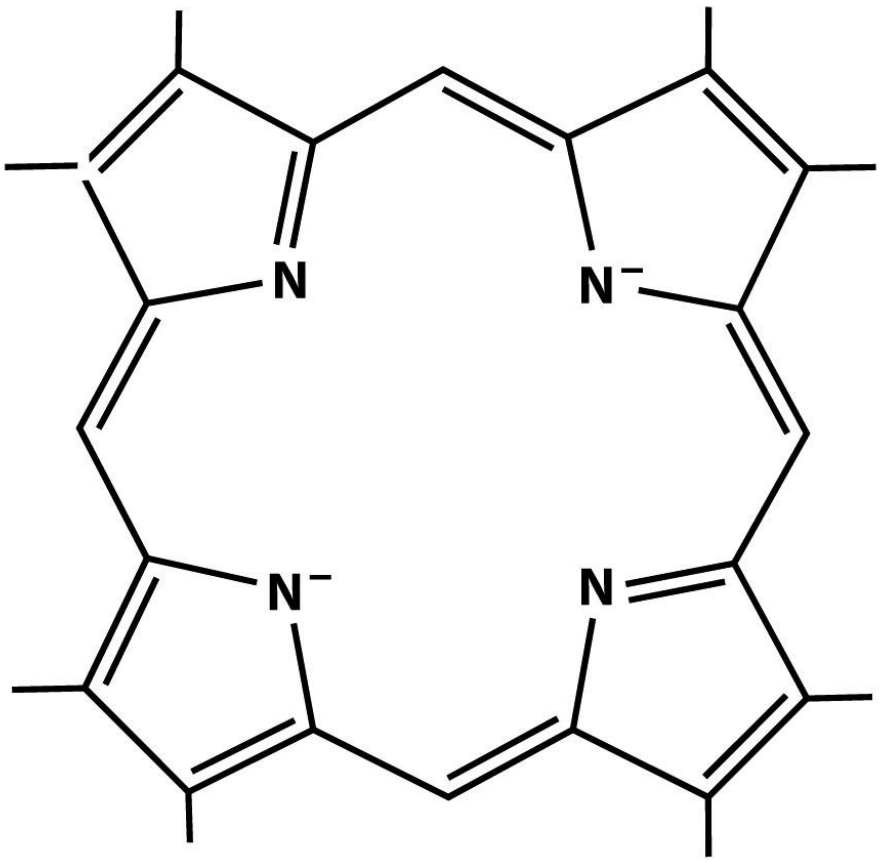
Co–C bond



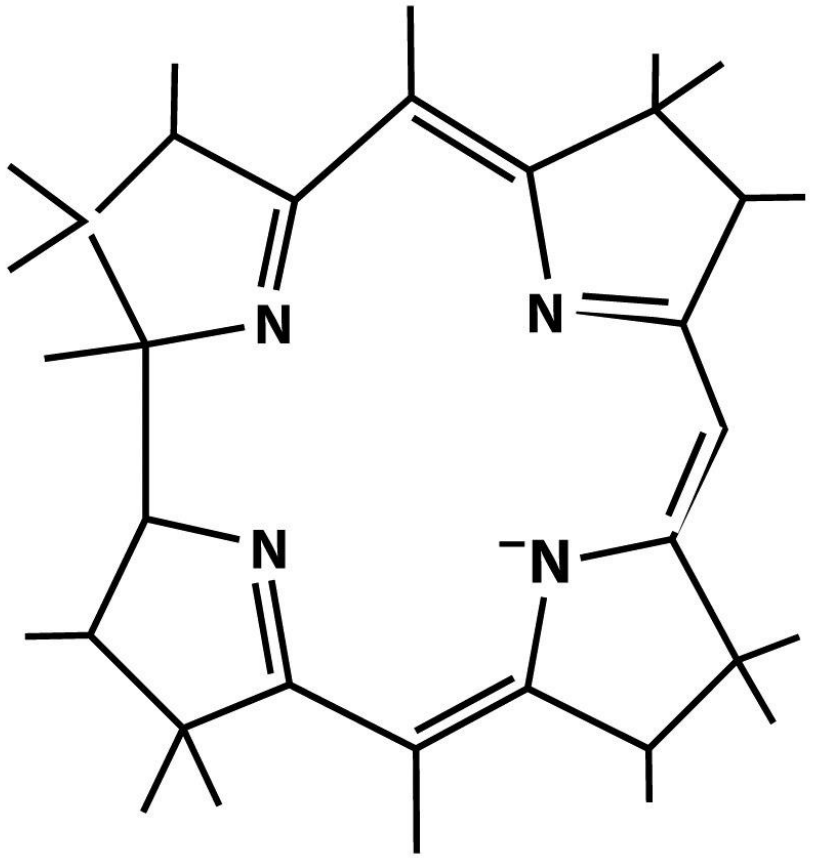
Dorothy Hodgkin, Chemistry Nobel laureate in 1964 for solving the X-ray structure of coenzyme B_{12}

Coenzyme B_{12}

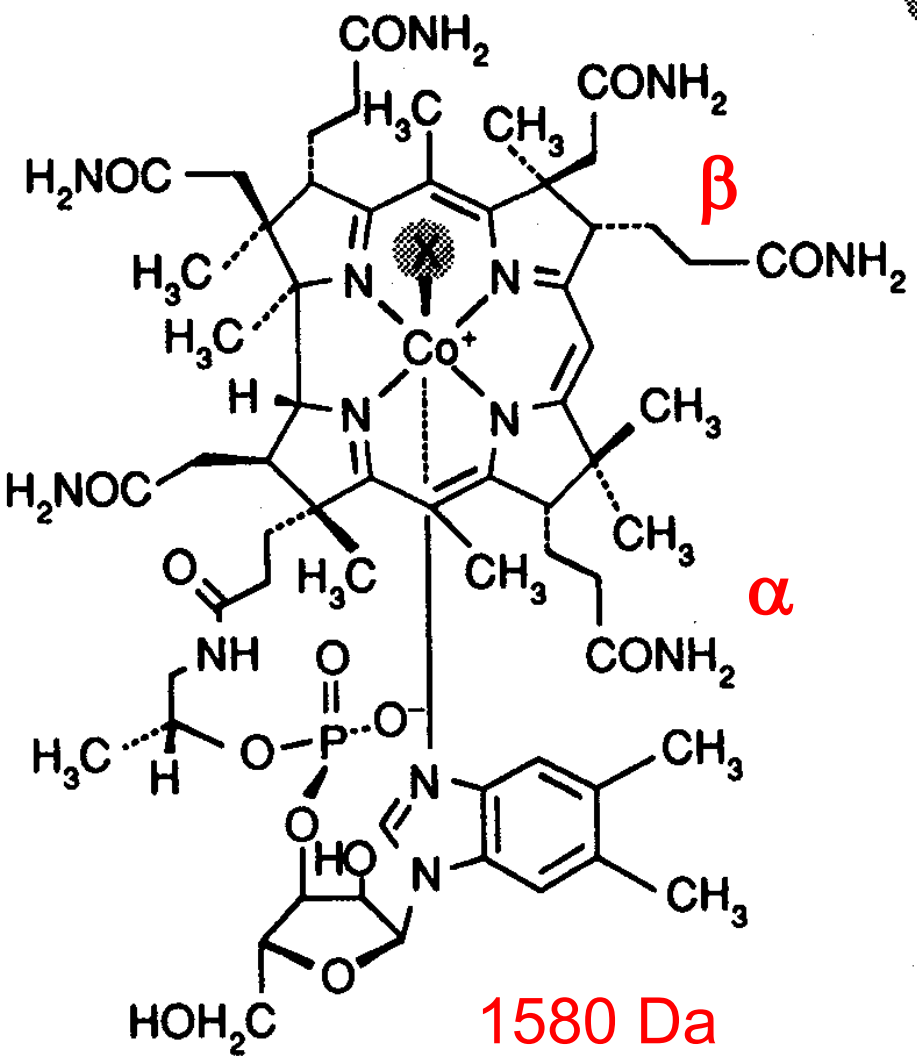
5′-deoxyadenosylcobalamin



Porphyrin^{2-}



Corrin^{-}



1580 Da

= CH_3 : methylcobalamin (MeCbl or MeB_{12})

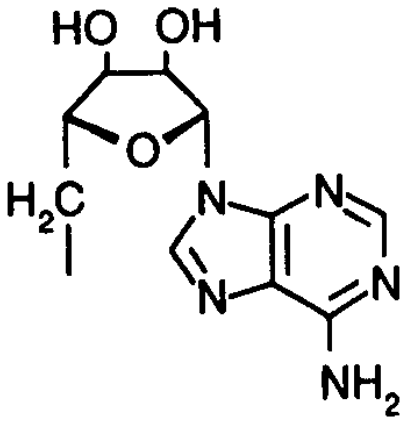
CN : cyanocobalamin (vitamin B_{12})

OH : hydroxycobalamin

H_2O : aquacobalamin

R : 5'-deoxyadenosyl-cobalamin (coenzyme B_{12}, AdoCbl or $AdoB_{12}$)

R = 5'-deoxyadenosyl



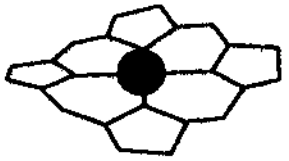
7 amidic lateral chains,
9 chiral centers

in-plane coordination
(side view)

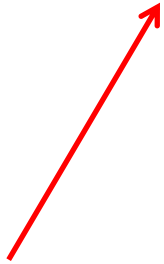
out-of-plane coordination
(side view)

'doming' of the
macrocycle

saddle-shaped
macrocycle



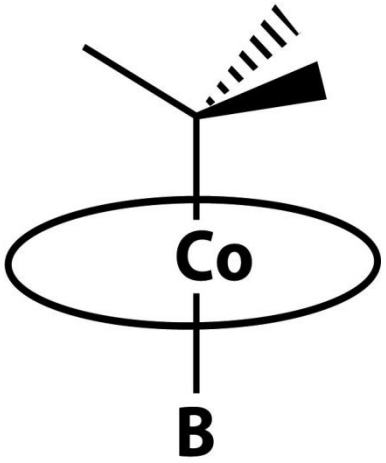
'ruffling' of the
macrocycle



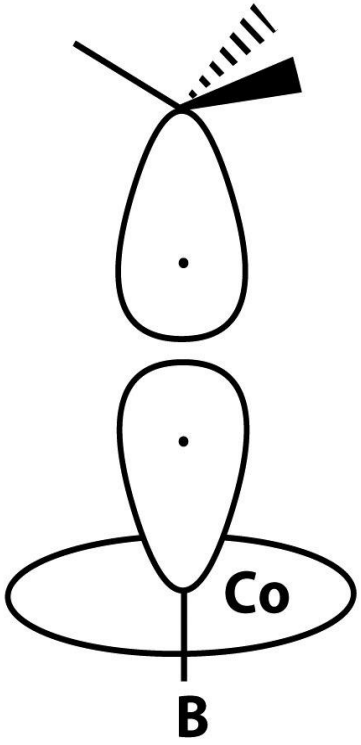
Distortion in the cobalamin

Co is always low spin

Co(III) d^6



C. N. = 6

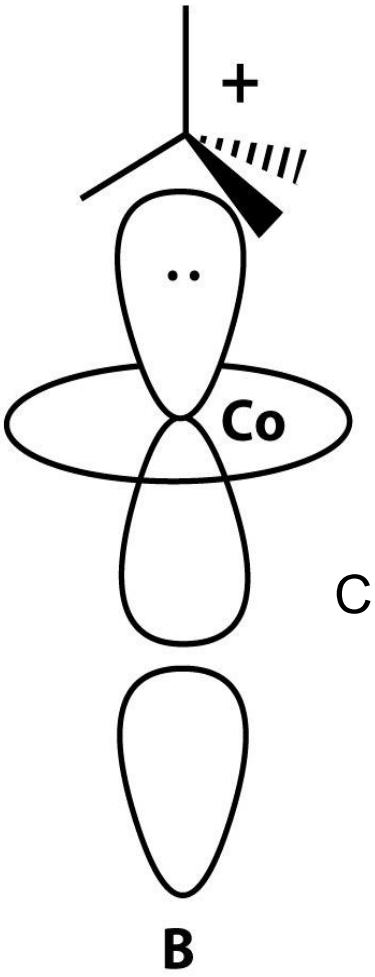


Co(II) d^7

C. N. = 5

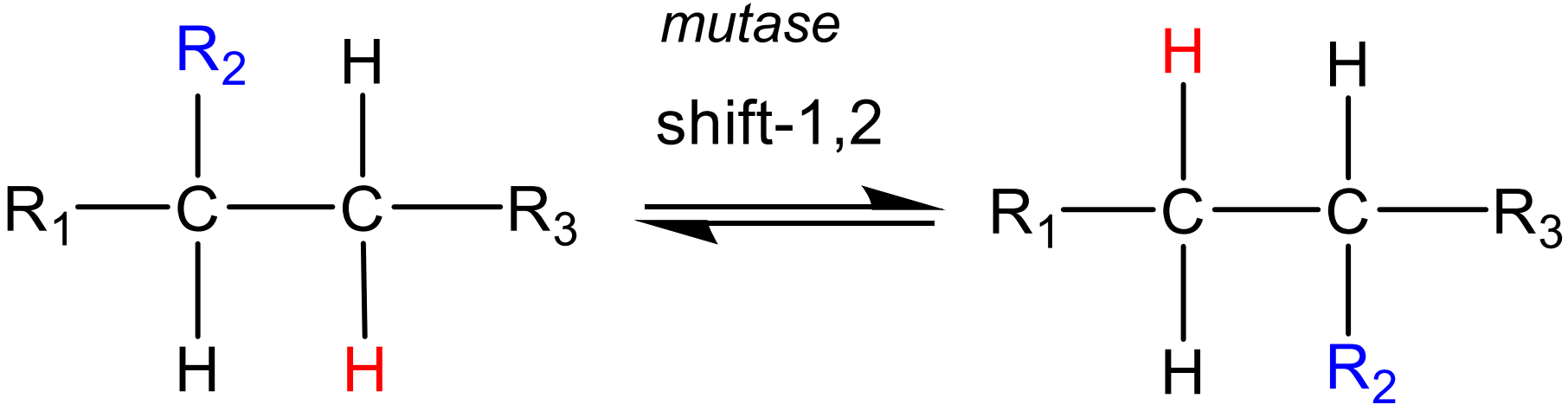
super-nucleophyle

Co(I) d^8



C. N. = 4

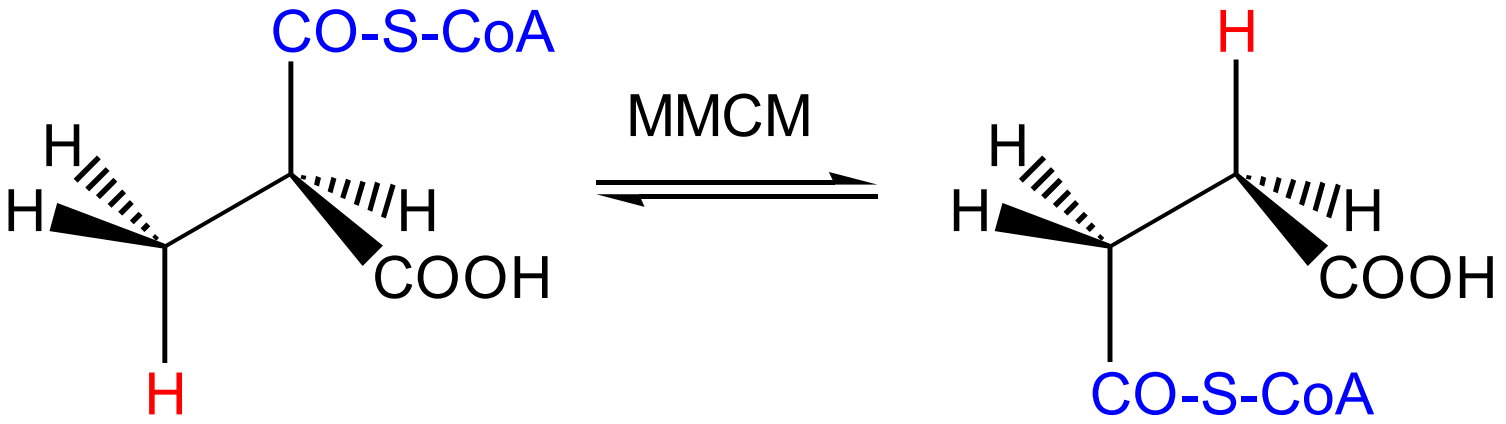
Reactions catalyzed by B_{12} coenzyme



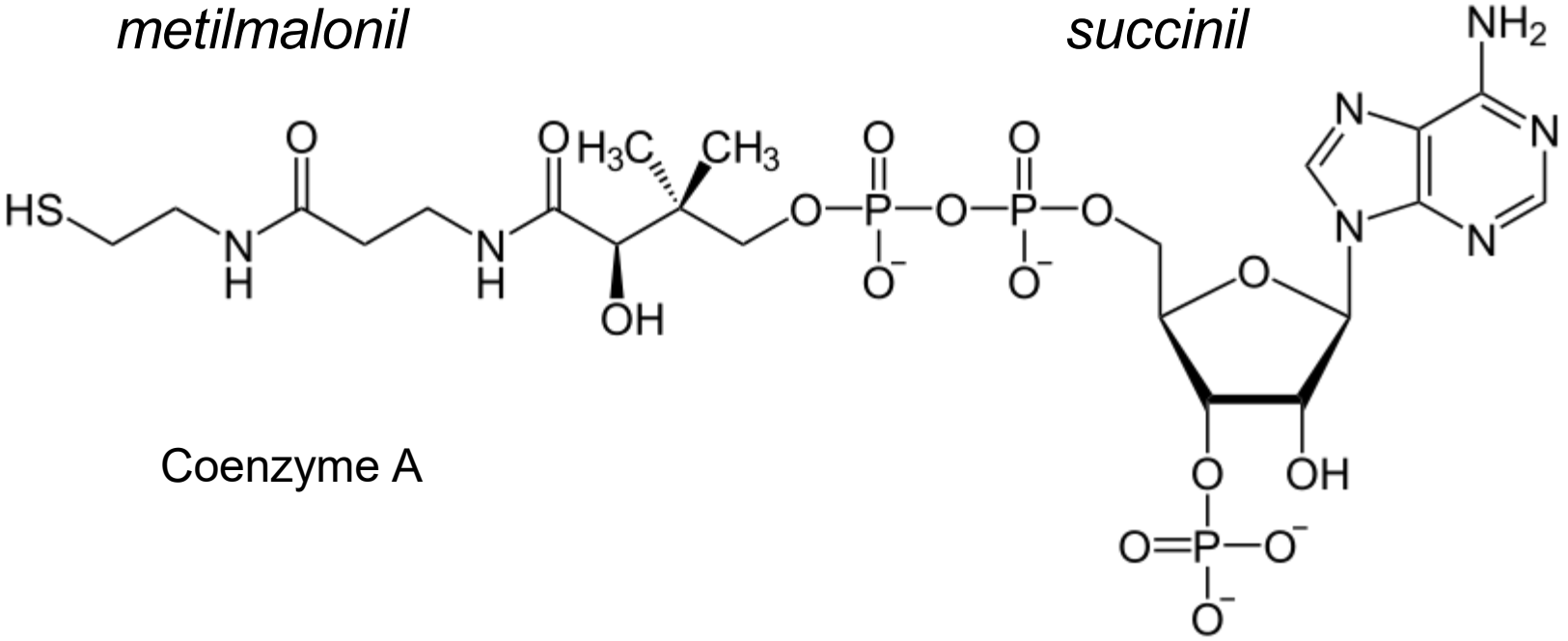
Enzyme	**R_1**	**R_2**	**R_3**
Diol dehydratase	CH_3	OH	OH
Ethanolamine deaminase	H	NH_2	OH
Glutamate mutase	H	$CH(NH_2)COOH$	COOH
Glycerol dehydratase	CH_2OH	OH	OH

MethylMalonyl-Coenzyme A-Mutase

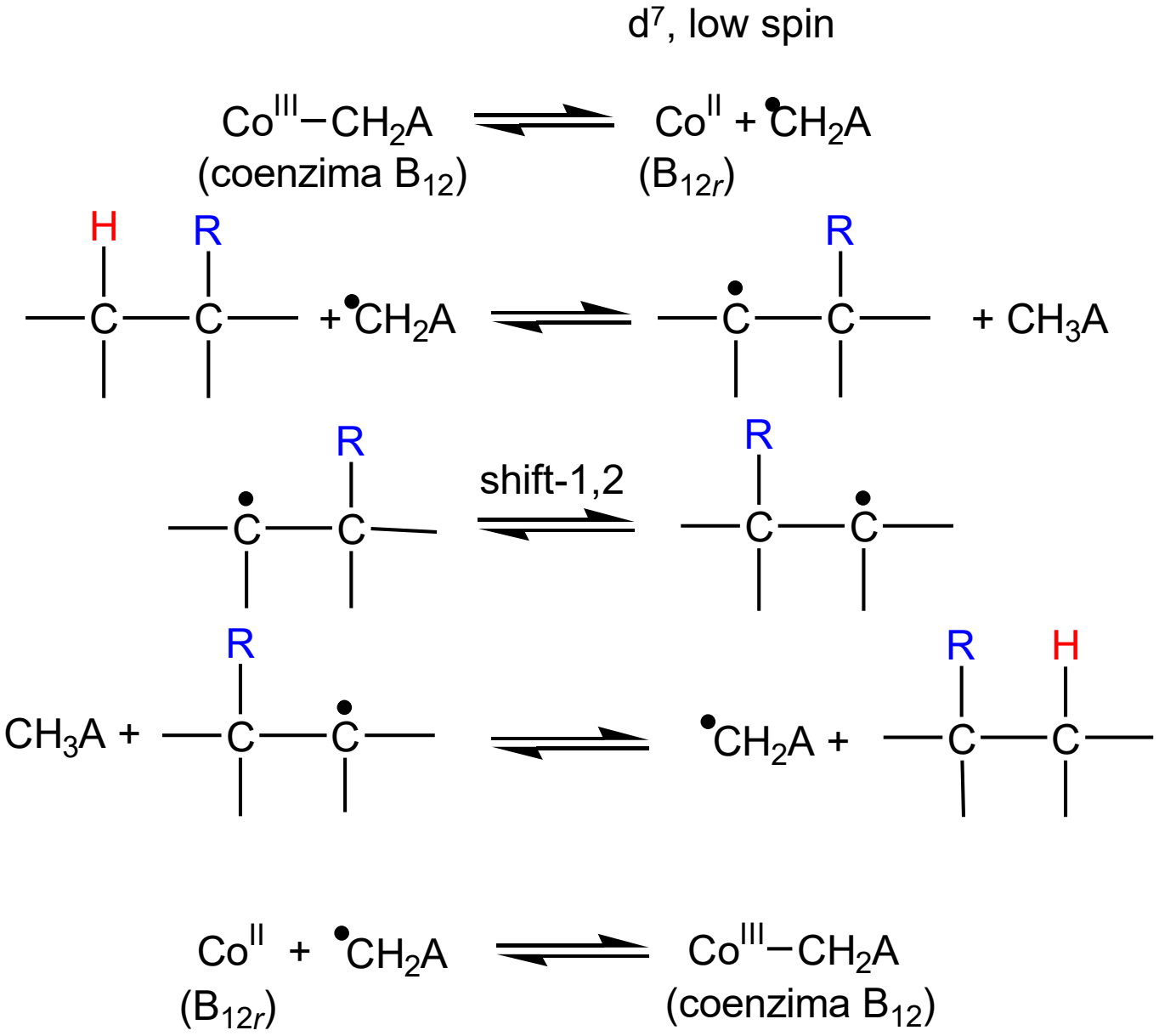
(succinyl-CoA is crucial for DNA synthesis within red blood cell precursors)



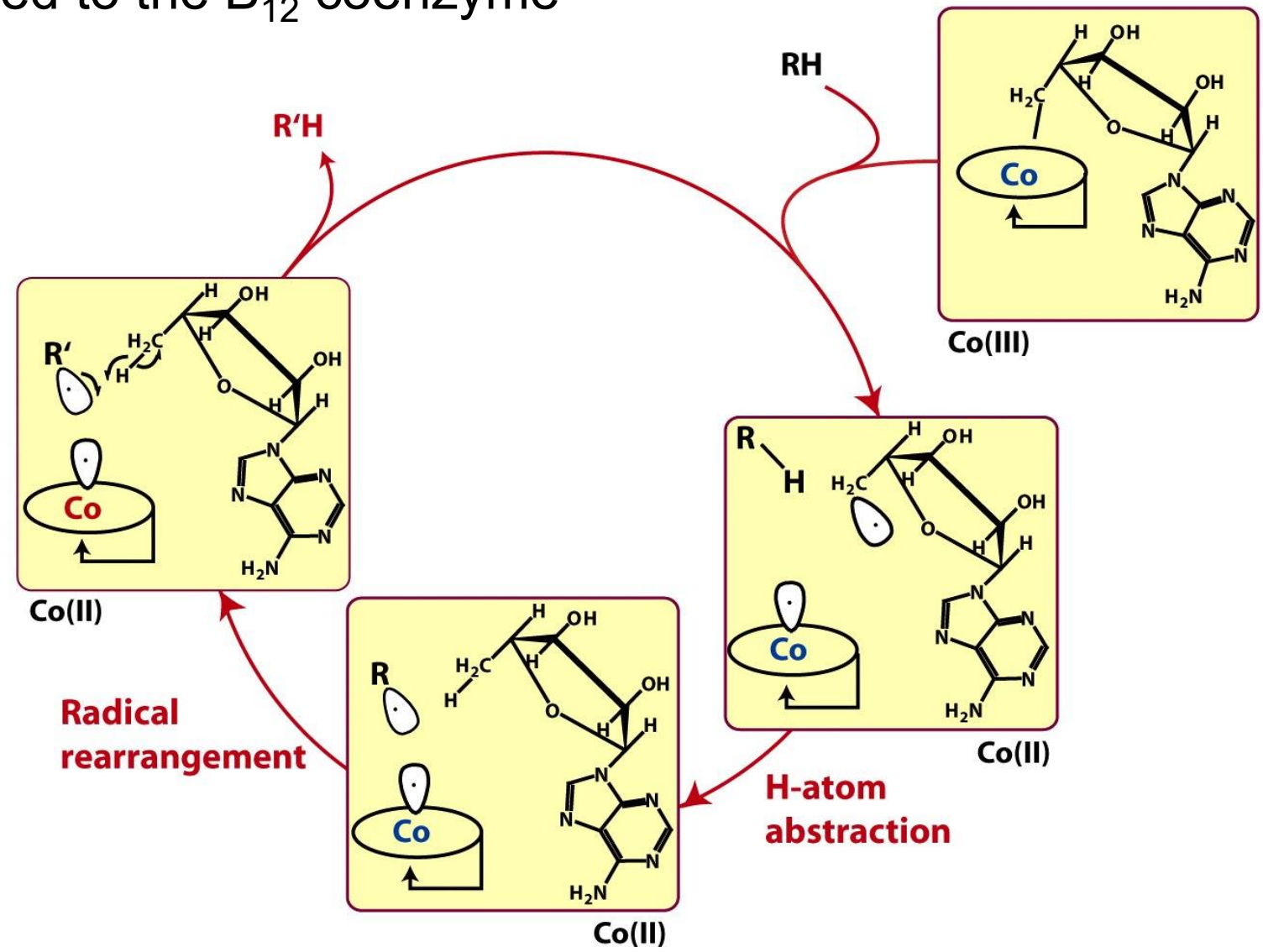
metilmalonil *succinil*



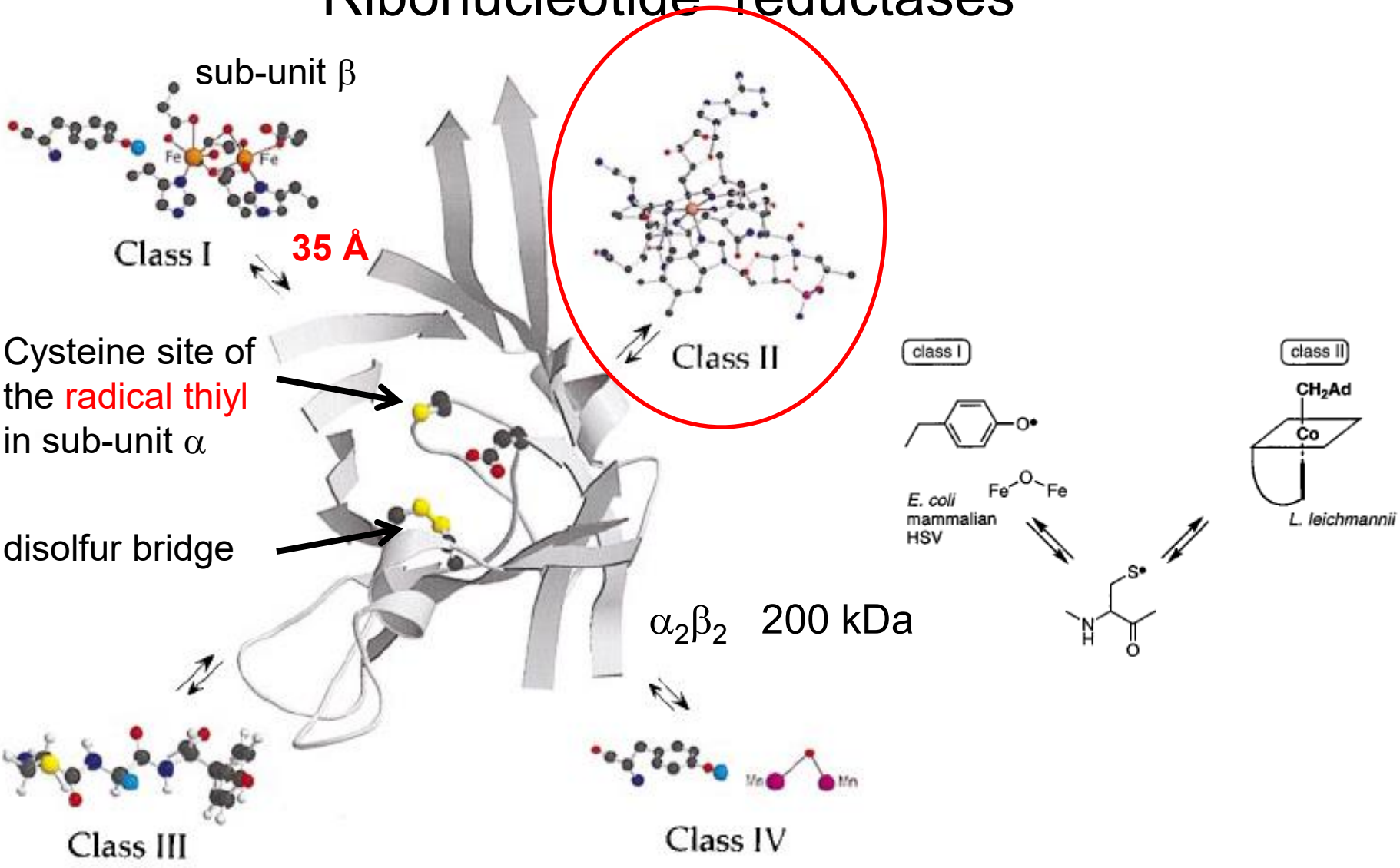
Coenzyme A


d7, low spin
Co^III–CH2A
(coenzima B12)
Co^II + •CH2A
(B12r)
H
R
+ •CH2A
+ CH3A
shift-1,2
CH3A +
•CH2A +
Co^II + •CH2A
(B12r)
Co^III–CH2A
(coenzima B12)

The cleavage of the Co–C is 10^{12} times faster in the full enzyme compared to the B_{12} coenzyme

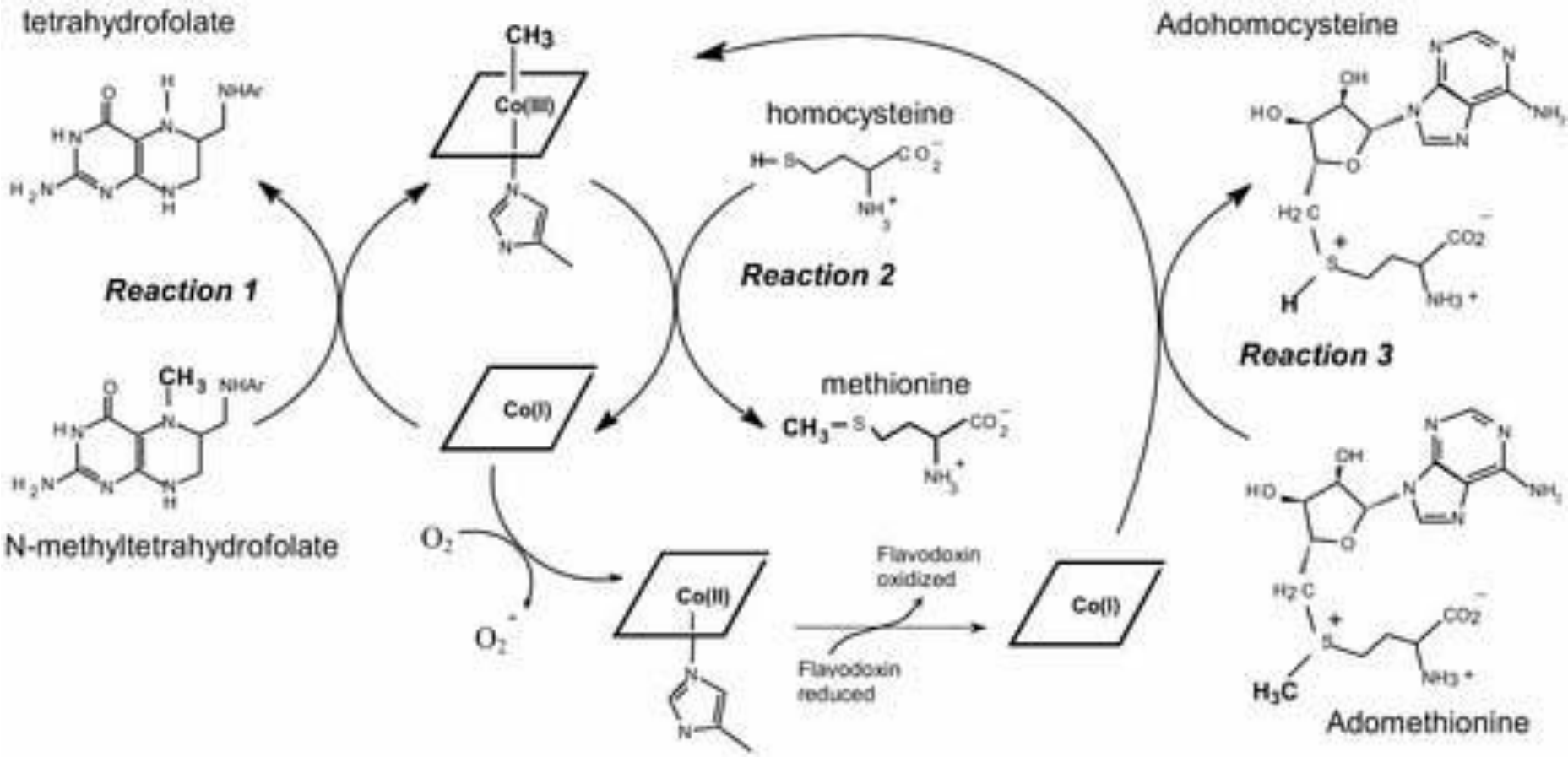


Active site and metal cofactors in different classes of Ribonucleotide reductases



Methylcobalamin: cofactor in Methionine Syntase

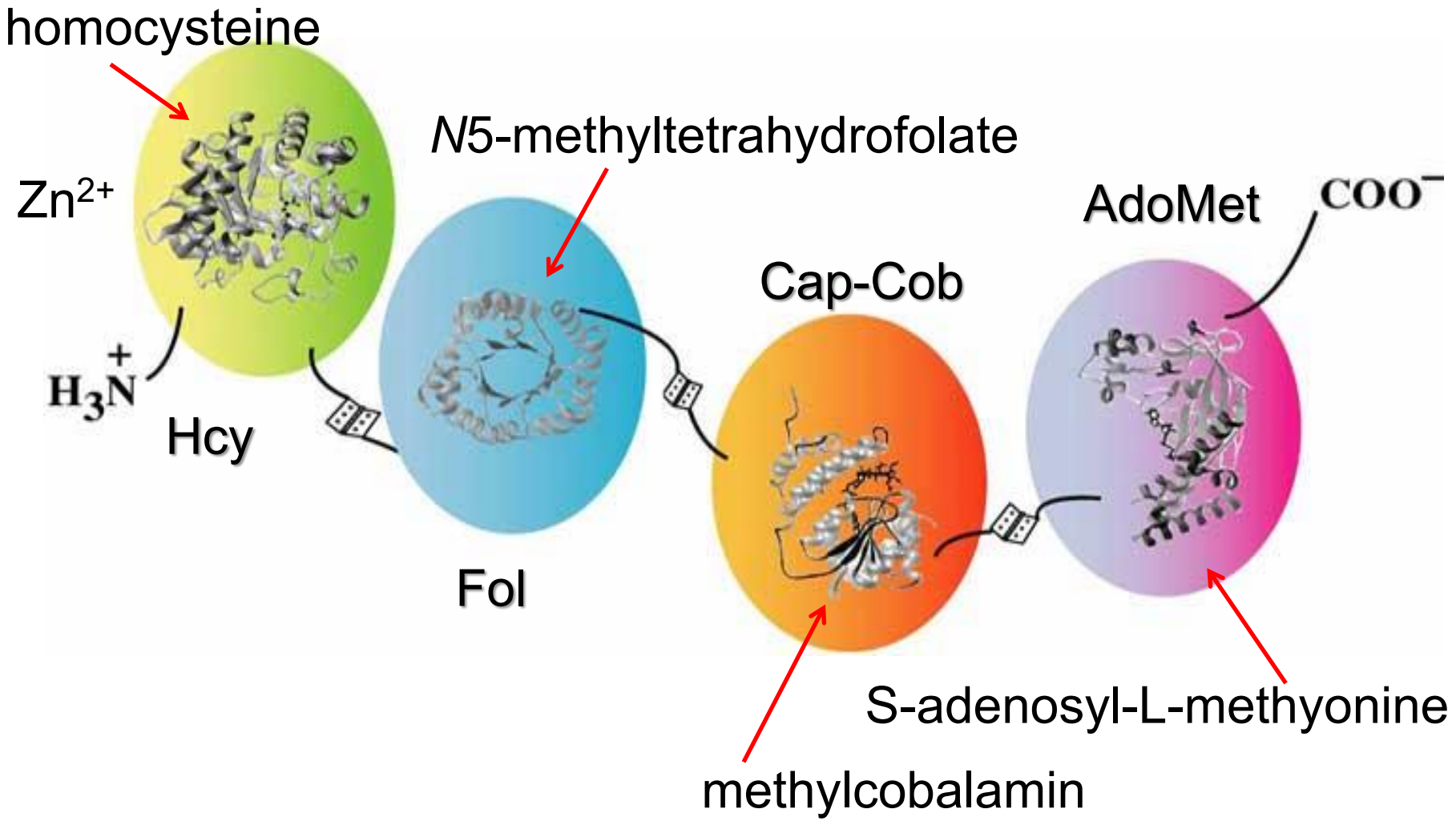
Essential enzyme for the metabolism of aminoacids in the liver



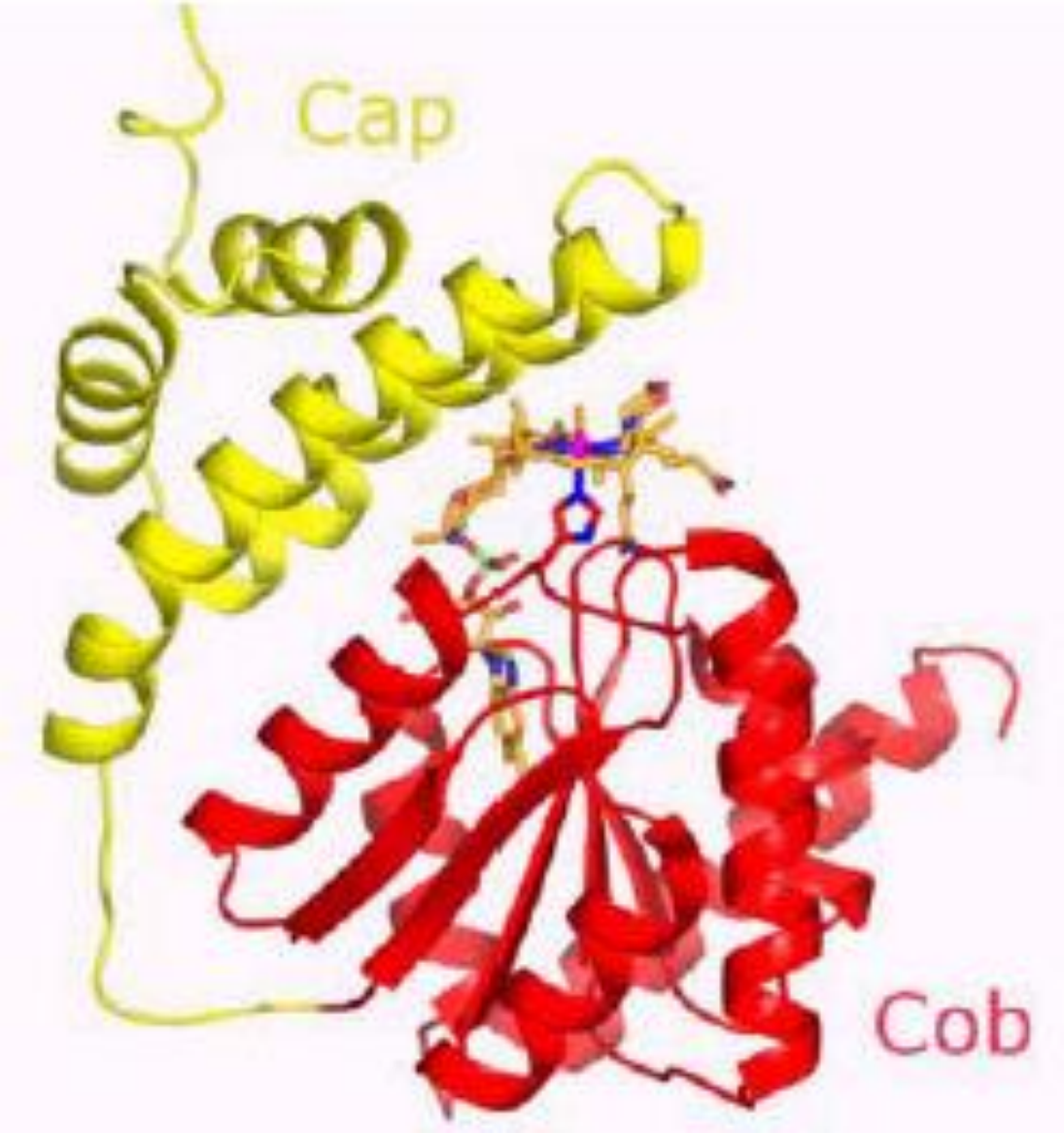
S-adenosyl-L-methionine

Methyl is transfered as CH_3^+

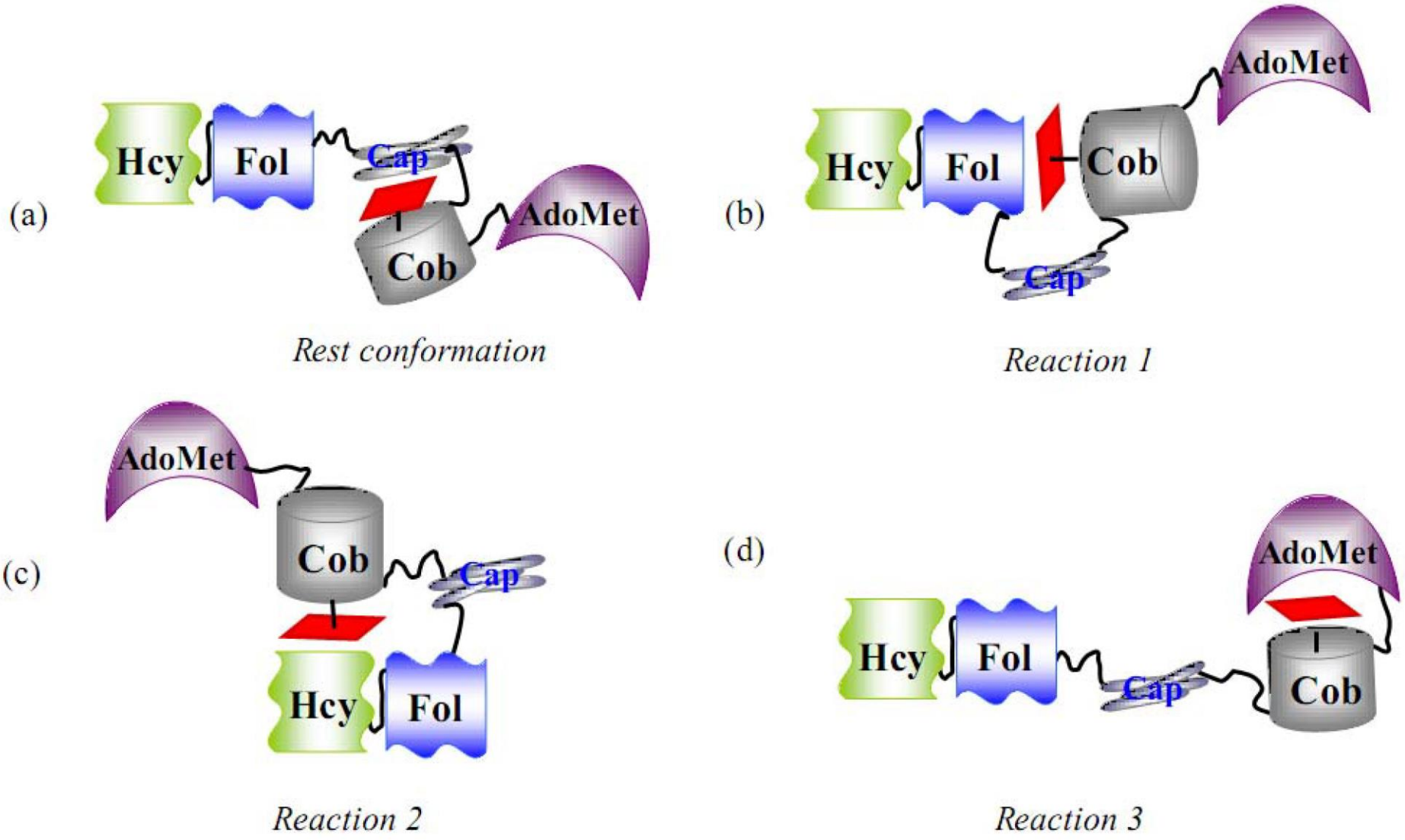
The four domains of Methyonine Syntase



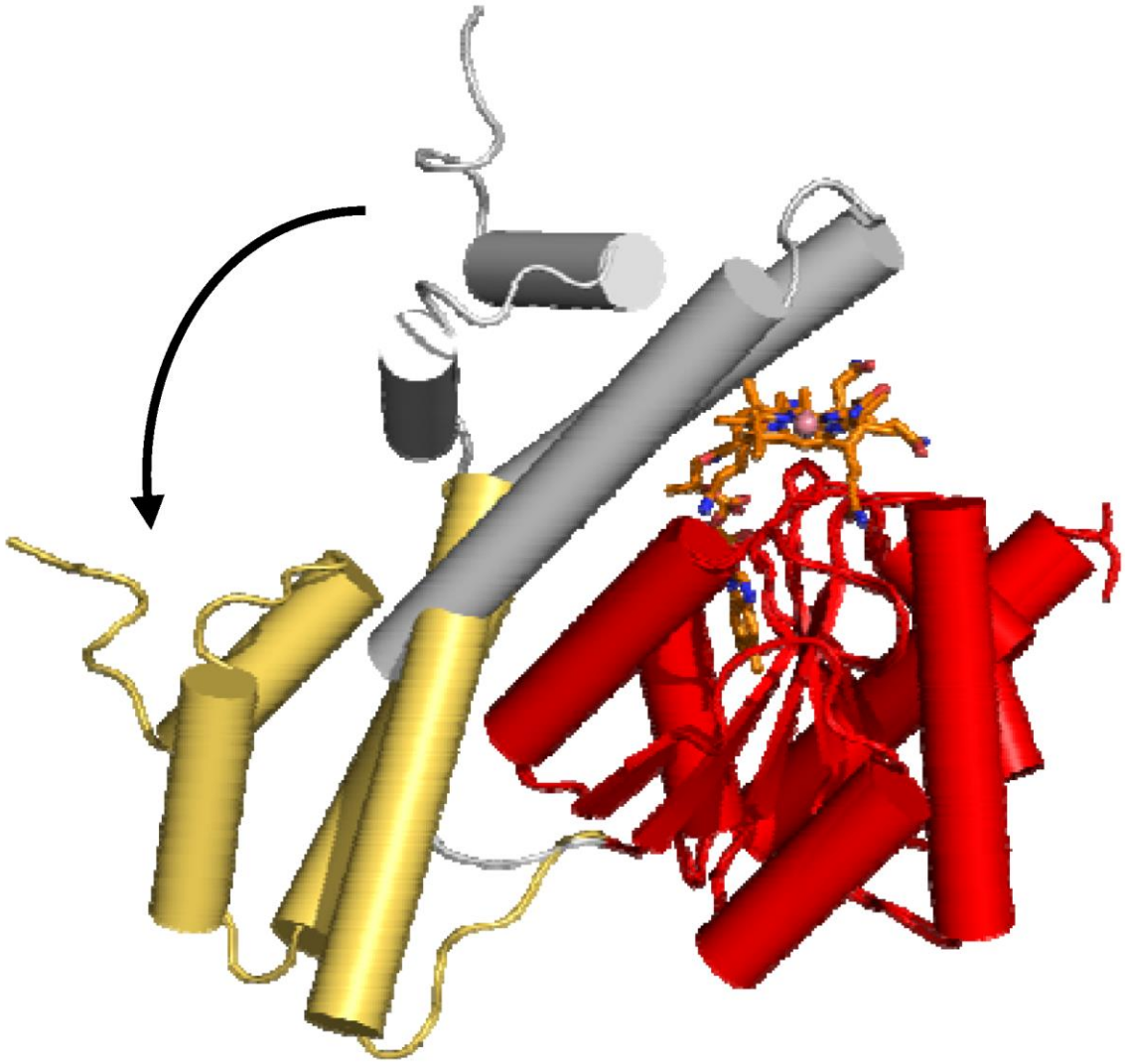
Methylcobalamin in Cap-Cob: *base-off/His-on*



Conformational changes in methyonine syntase



Conformational changes in the Cap sub-domain

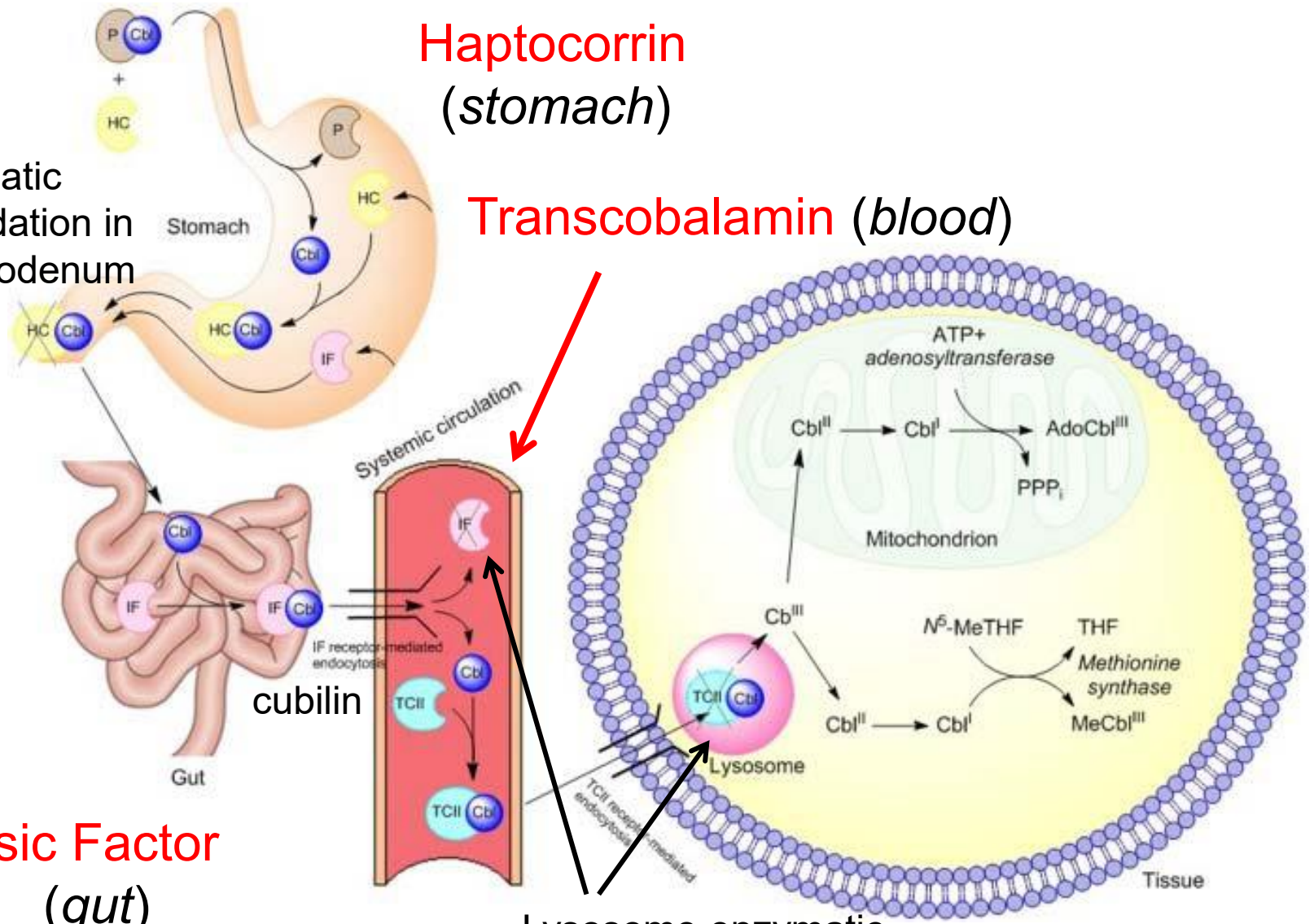


The 3 proteins for the uptake and transport of Cobalamin

Haptocorrin
(*stomach*)

enzymatic degradation in the duodenum

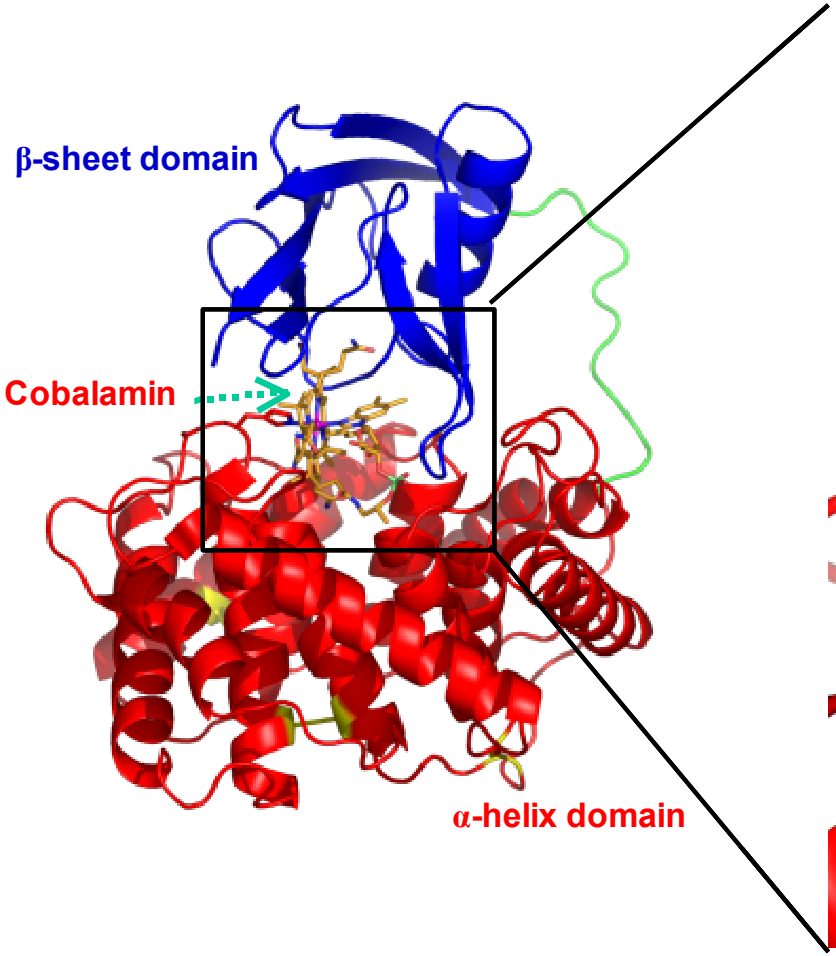
Transcobalamin (*blood*)

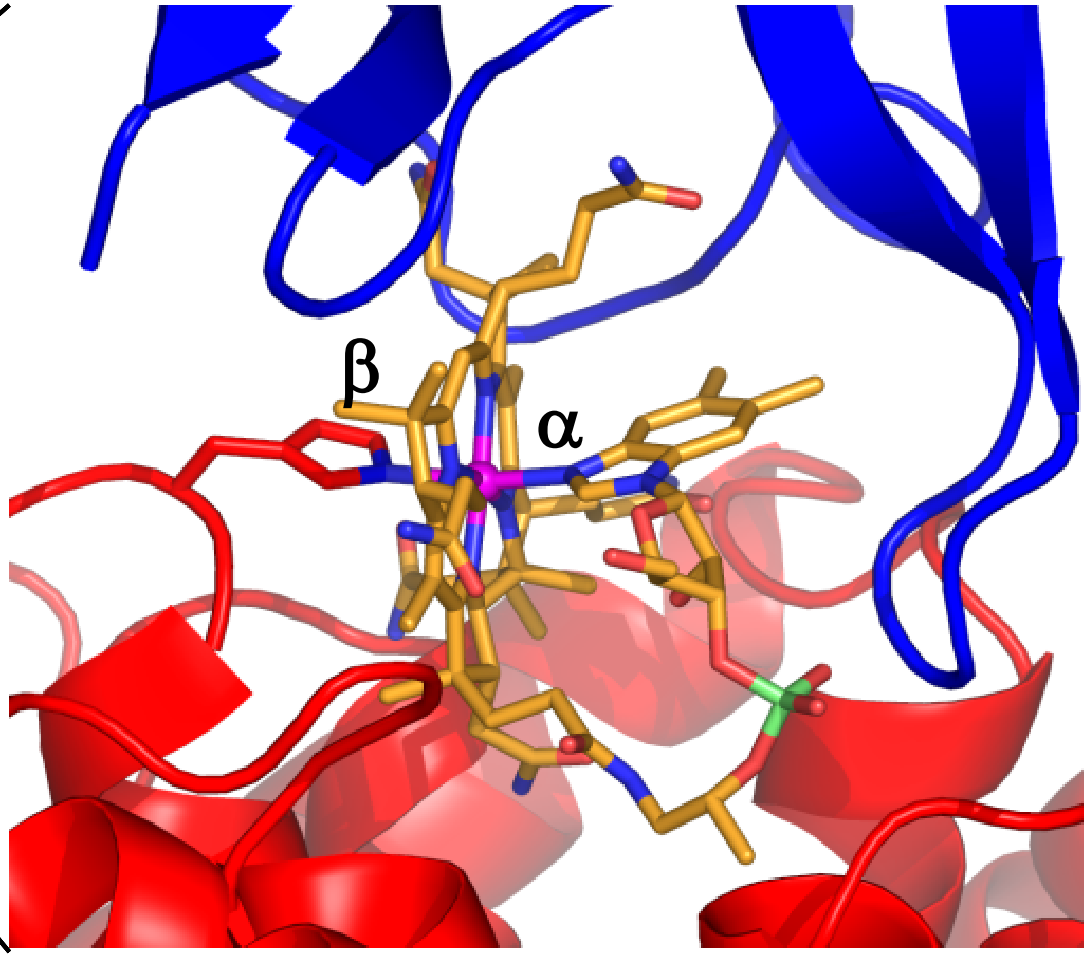


Intrinsic Factor
(*gut*)

Lysosome enzymatic degradation

X-ray structure of TC+Cobalamin (2006)

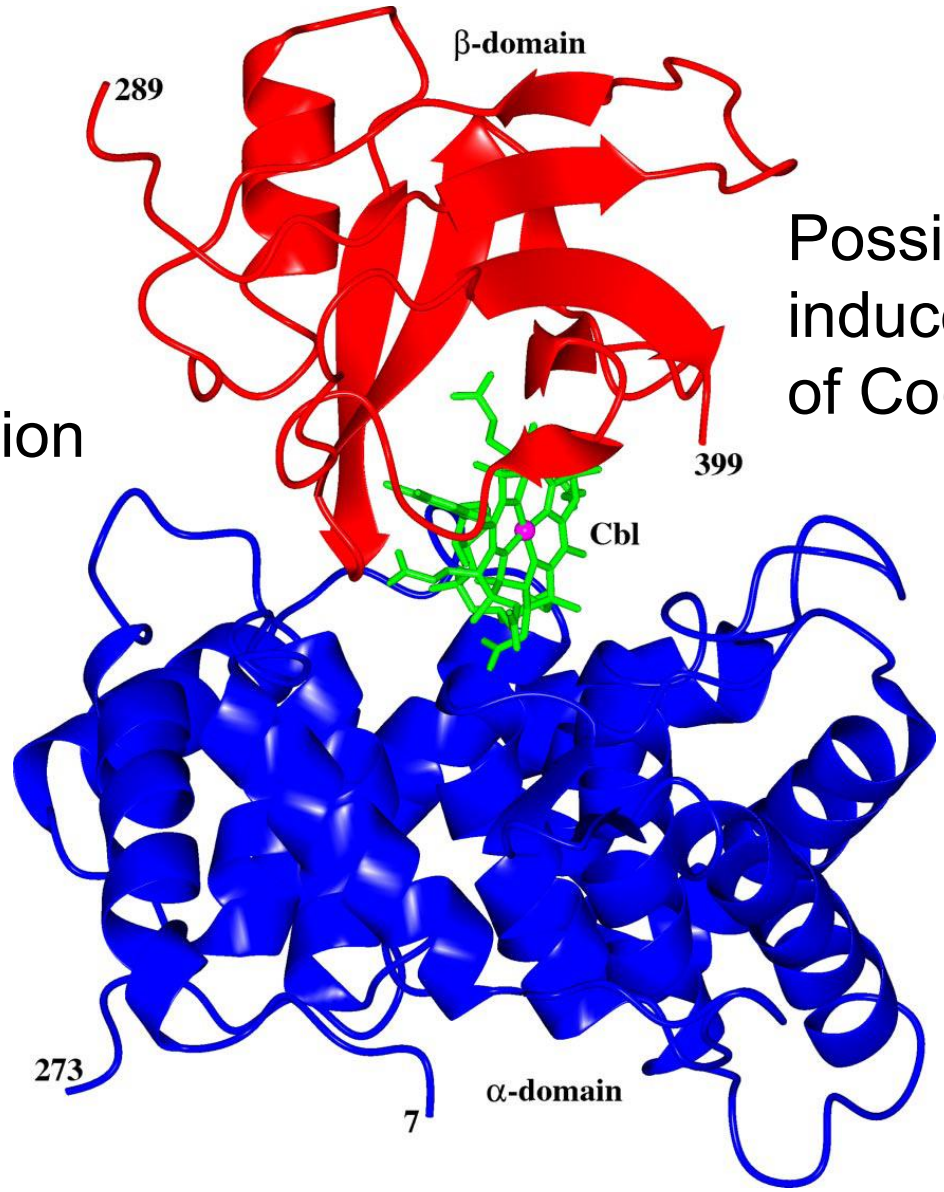




Coordination *base-on/His-on* (on β)

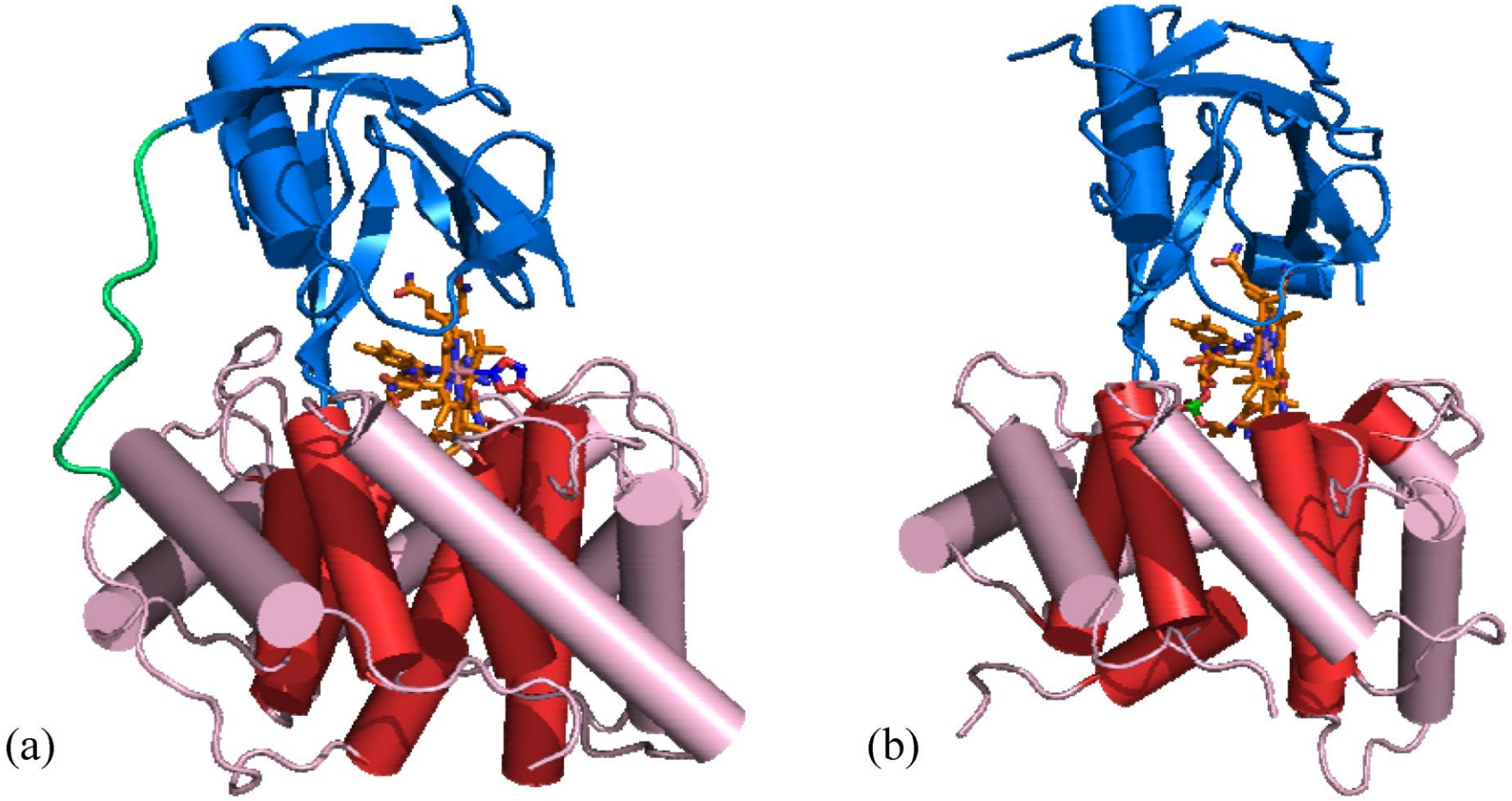
X-ray structure of IF-Cobalamin (2007)

base-on coordination



Possible X-ray induced reduction of Co(III) to Co(II)

Comparison between the structures of TC-Cbl (a) and IF-Cbl (b)



Adduct of IF-Cbl with CUB_{5-8} receptors of cubilin