Acid–base and metal ion-binding properties of thiopyrimidine derivatives

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The thionucleoside 2-thiocytidine (C2S) as well as the thiouridines (US) occur in Nature, especially in transfer RNAs, and they also receive attention in diverse fields like nanotechnology and drug research. If (C2)O in cytidine (Cyd) is replaced by (C2)S to give the thio analogue C2S, the release of H + from (N3)H in H(C2S) + (p K a =ă3.44) is facilitated somewhat [H(Cyd) + ; p K a =ă4.24], yet, the deprotonation of the (C4)NH 2 group is much more affected: the p K a decreases from ca. 16.7 in Cyd to 12.65 in C2S. This is because the amino-thione tautomer dominating in the neutral C2S, transfers into the imino-thioate form, which has the charge largely localized on (C2)S − . As a consequence, the M(C2S) 2+ species (M 2+ =ăZn 2+ or Cd 2+) transfer very easily into their deprotonated M(C2Să−ăH) + forms. This reaction is extremely facilitated by M 2+ coordination at (C2)S − and occurs already at a pH slightly above 3. It is shown that the (C2)S M 2+ coordination dominates to more than 99% in both the M(C2S) 2+ and the M(C2Să−ăH) + complexes; their structures, including chelate formation with the participation of N3, are evaluated. In 2-thiouridine (U2S), 4-thiouridine (U4S), and 2,4-dithiouridine (U2S4S), the release of H + from (N3)H, compared to Urd (p K a =ă9.18), is facilitated by ca. 1 to 2 p K units, the charge being largely localized on the (C)S sites; this leads with (U4Să−ăH) − and (U2S4Să−ăH) − to the reduction of Cu(II) to Cu(I), transforming the thiolate into a disulfide. In Cu(U2Să−ăH) + Cu(II) is stable, most likely due to steric constraints inhibiting disulfide formation. The stability of the M(USă−ăH) + complexes with Ni 2+ , Cu 2+ or Cd 2+ is enhanced by about 1.3 to 2ălog units compared to the corresponding uridinate complexes. The properties of the biologically relevant Zn(USă−ăH) + are expected to be between those with Ni 2+ and Cd 2+ . The relatively high affinity of the (C)S sites for these M 2+ is reflected in the 2-thiouridine 5′′-monophosphate (U2SMP 2−) and 4-thiouridine 5′′-monophosphate (U4SMP 2−) complexes, M 2+ being located to more than 99% at the thiouracil residue and only traces are coordinated at the phosphate group. In the N3-deprotonated Cu[(U2Să−ăH)MP] − species the anti conformer is partly turned into the syn one allowing thus a formation degree of about 60% of the macrochelate formed by (C2)S − and the phosphate group. The corresponding coordination pattern also seems to hold for Cd[(U2Să−ăH)MP] − , though the formation degree of the macrochelate is lower. No macrochelate formation is detected for Ni[(U2Să−ăH)MP] − , as well as for Ni[(U4Să−ăH)MP] − and Cd[(U4Să−ăH)MP] − . The reasons for the indicated coordination patterns are discussed, as well as the biological implications of the summarized results, especially with regard to tRNAs.
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