Inorg. Chem. **2005**, *44*, 1950–1954

Metal Ion Catalysis of Natural Products Transformations. Novel Aldopentose Disproportionation Reactions Catalyzed by Rhodium(III)

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Received August 23, 2004

The detailed stoichiometry of the reaction between the aldopentoses, ribose, arabinose, lyxose, and xylose, and the cis rhodium(III) complex of the macrocyclic tetraamine ligand *rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane in weakly acidic aqueous solution has been studied by ^{13}C NMR, using deuterium- and carbon-13-labeled substrates. The overall process is a catalytic disproportionation reaction, in which two aldopentose molecules are transformed into the corresponding alditol and aldonolactone, both with an unchanged configuration around carbon atoms 2, 3, and 4. The mechanism of this reaction is suggested to involve coordination of a hydrated and an unhydrated substrate molecule through their carbon-1 bound oxygen atoms followed by a hydride shift from the hydrated to the unhydrated substrate. This disproportionation process is subsequently followed by aquation of the reaction product to give the free alditol and a mixture of the aldonic acid and the corresponding aldonolactone. Concurrently with the aquation reaction, incorporation of solvent hydrogen at the carbon-1 atom of the alditol is also observed for the rhodium-coordinated alditol reaction product.

Introduction

Interactions between metal ions and carbohydrates range from simple outer-sphere interactions through formation of inner-sphere complexes to complicated carbohydrate rearrangements catalyzed by complex formation, as recently reviewed.[1] This latter type of reactivity involves carbohydrate epimerizations and carbohydrate skeleton rearrangements catalyzed by molybdenum(VI), nickel(II), and a number of other metal ions.[1−5]

An entirely different type of carbohydrate reactivity, recently demonstrated, was the transformation of glyceraldehyde and 1,3-dihydroxyacetone into coordinated chelate lactate, in which one hydrogen atom of the methyl group originated from the solvent water.[6,7] This process was induced by both chromium(III) and rhodium(III) complexes of the macrocyclic tetraamine ligand *rac*-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane, cyc*b*. The detailed stoichiometry of these reactions was characterized and a mechanism was suggested, which was subsequently shown also to be valid for transformation processes of other carbohydrates initiated by chromium(III).[8] These latter reactions give chelate complexes of deprotonated saturated and unsaturated 2-hydroxycarboxylic acids by intramolecular redox reactions as shown in Scheme 1.

Investigations of the chromium(III) reactions were limited by the paramagnetism of chromium(III) which prevented NMR measurements on the complexes. An important aspect of the present work, involving diamagnetic rhodium(III) complexes, was attempts to characterize the reactive intermediates in greater detail. Eventually, however, it turned out that, contrary to the results for the three-carbon atom substrates where the same products are formed by the chromium(III)- and rhodium(III)-catalyzed reactions, products

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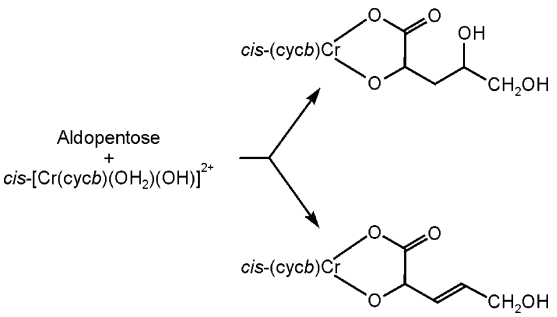
10.1021/ic0400989 CCC: $30.25
Published on Web 02/09/2005

Scheme 1



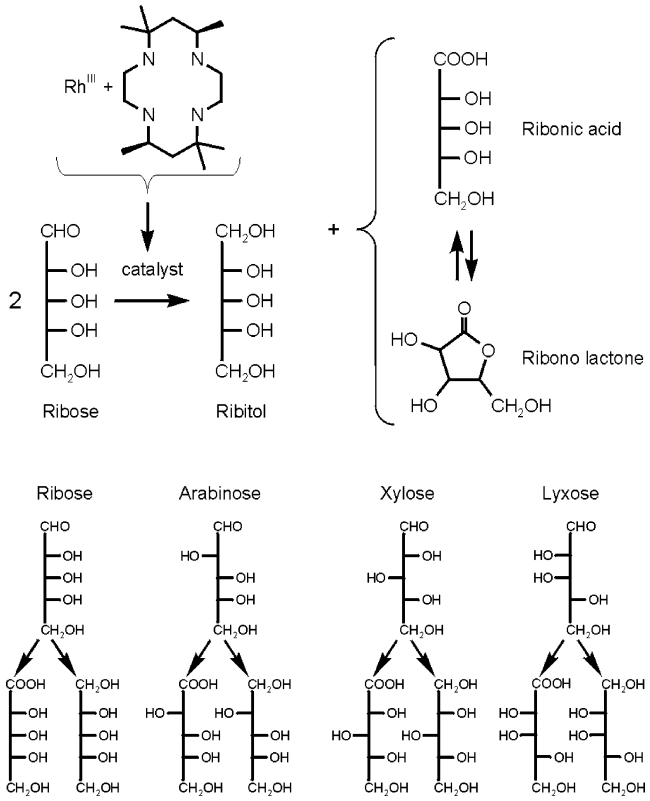
different from those obtained by the chromium(III)-catalyzed aldopentose transformations were found for the rhodium(III)-catalyzed process. The overall reaction type was still a disproportionation reaction, but intramolecular for chromium(III) and intermolecular for rhodium(III), resembling the well-known Cannizzaro reaction, which takes place in basic solution by an intermolecular hydride transfer reaction.[9]

Results and Discussion

Rhodium(III)-Catalyzed Ribose Transformations. The reaction of ribose in the presence of *cis*-[Rh(cyc*b*)$(OH_2)_2]^{3+}$ in dilute nondeuterated perchloric acid was followed by ^{13}C NMR. Initially, the spectral changes are very complicated, which is understandable when it is realized that coordination of one substrate molecule to the Rh(cyc*b*)-unit will give a mixture of diastereomers. This gives rise to at least $2 \times (2 \times 8 + 5) = 42$ new ^{13}C-resonances even in the simple case where the configuration of the complex, including the conformation of the macrocyclic ligand, is unchanged and the substrate is coordinated in only one form. Prolonged standing produces a simpler resonance pattern, characterized by the appearance of 13 ^{13}C-resonances, correlated with the disappearance of the ribose resonances. These 13 new resonances originate apparently from three products responsible for 5, 5, and 3 resonances, respectively.

The product responsible for the three resonances with an apparent 2:2:1 intensity ratio was tentatively identified from the chemical shifts as ribitol.[10] This tentative identification was subsequently verified by the addition of an authentic ribitol sample to the reaction mixture. The product(s) responsible for the remaining 2×5 ^{13}C-resonances was similarly identified as a mixture of ribonic acid and ribono lactone. Again, the identification was initially based upon the chemical shift of the positions of the ^{13}C-resonances of the lactone[10] and was subsequently substantiated by the addition of an authentic sample of the lactone to the reaction mixture. In basic solution, the resonance pattern of the reaction mixture is simplified to eight ^{13}C-resonances, corresponding to three resonances from ribitol and five resonances from the ribonate anion. Acidification of such a solution shows the expected time-dependent equilibration between the ribonic acid, first formed by protonation, and its γ-lactone, which is ultimately the major component.[10] The overall stoichiometry of the reaction consequently corresponds to an intermolecular redox reaction between two ribose molecules, catalyzed by the rhodium(III) complex as shown in Scheme 2.

Scheme 2



The appearance of carboxylic acid derivatives was also the case for the chromium(III)-catalyzed reactions.[8] Contrary to the significant rearrangements found for these latter reactions, the rhodium(III)-catalyzed aldonic acid reaction product has maintained the stereochemical identity around carbon atoms 2, 3, and 4, as demonstrated by the simplified transformation stoichiometry in the lower part of Scheme 2.

Rhodium(III)-Catalyzed Aldopentose Transformations. An identical pattern of reactivity is seen for the three other aldopentoses, arabinose, xylose and lyxose. A mixture of alcohol and carboxylic acid, both with unchanged configurations around carbon atoms 2, 3, and 4, is produced. Thus, xylose gives the symmetrical xylitol alcohol, characterized by three ^{13}C-resonances, whereas both arabinose and lyxose give the same unsymmetrical arabinitol alcohol, showing the expected five ^{13}C-resonances. The tentative structural assignments of the alcohols were verified by ^{13}C NMR after addition of authentic samples of the compounds in question to the reaction mixtures. The tentative structural assignments of the carboxylic acid/lactone mixtures were based upon literature values of ^{13}C-resonance positions for the aldonolactones.[10]

Rhodium(III)-Catalyzed Transformations of Deuterated and ^{13}C-Labeled Ribose. To characterize further the detailed stoichiometry of these processes, the reactions of

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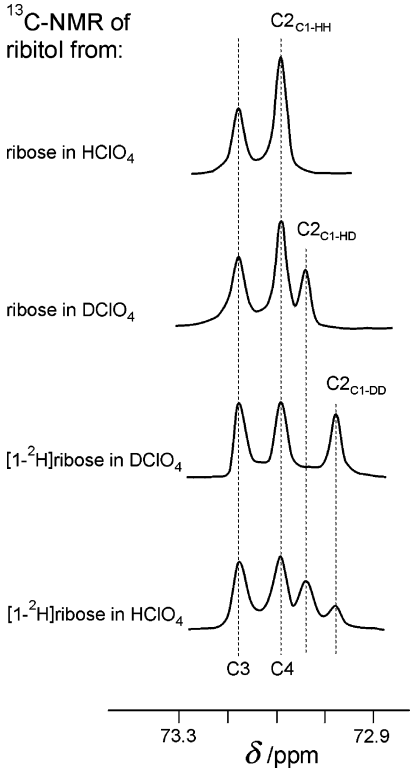


Figure 1. ^{13}C NMR spectra of ribitol reaction products in the region of the secondary alcohol groups around $\delta \approx 72-73$ ppm.

ordinary and of 1-D labeled ribose were investigated in ordinary and in deuterated 0.01 M perchloric acid. The resonance patterns of the ribonic acid/ribono lactone mixtures are the same for all four combinations of deuterated/nondeuterated solvents and deuterated/nondeuterated substrates, but the resonance patterns for the ribitol products are different. This is summarized in Figure 1 for the resonances of carbon atoms 2, 3, and 4.

It is evident that symmetrical ribitol is formed in the absence of deuterium, cf. Figure 1A. It is also evident that unsymmetrical products, with deuterium introduced at the carbon-1 atom, are formed in the presence of deuterium in either solvent or substrate, Figure 1B−D. It is also seen that carbon atoms 3 and 4 are not affected. It is further noted that a direct intermolecular transfer of the aldehydic hydrogen/deuterium atom takes place. In addition to this latter process also hydrogen/deuterium from the solvent is seen to be incorporated into the ribitol product, Figure 1C and D.

This partial solvent hydrogen/deuterium incorporation was further demonstrated by reacting carbon-1 and carbon-2 ^{13}C-labeled ribose in deuterated perchloric acid. The results of these experiments are shown in Figure 2.

The ^{13}C-spectrum of the carbon-1-labeled substrate again clearly shows partial deuterium incorporation in the ribitol product at this carbon atom, evidenced by a triplet with one component assumed to be obscured by the resonance from the undeuterated product. The value of the coupling constant, $^1J_{CD} \approx 21.7$ Hz, is similar to that seen for similar compounds. The ^{13}C-spectrum of the carbon-2-labeled substrate similarly demonstrates the solvent deuterium incorporation at the carbon-1 atom, here evidenced by the isomer shift caused

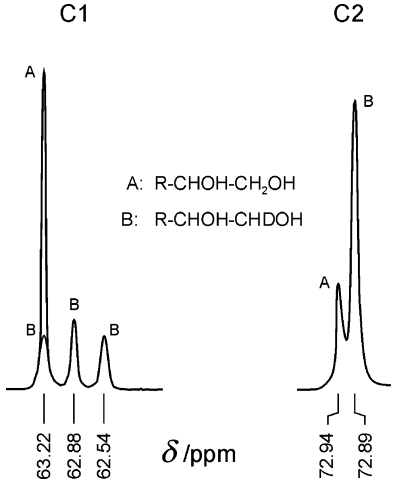


Figure 2. ^{13}C NMR spectra of ribitol reaction products from carbon-1 and carbon-2 ^{13}C-labeled ribose in deuterated perchloric acid.

by deuterium at the neighboring carbon-1 atom, identical to that seen in Figure 1. These experiments with ^{13}C-labeled riboses further show that the 5-atom aldopentose carbon skeleton is maintained unchanged in the reaction products. This is contrary to the reported interchange of the carbon-1 and carbon-2 atoms, which takes place in the epimerization reactions at the carbon-2 atom position catalyzed by molybdenum(VI)[3] and nickel(II).[4]

Finally, similar experiments were carried out with 2-D labeled ribose. This verified the suggested stoichiometric mechanism further, in that both the produced ribitol and the ribonic acid/ribono lactone mixture retained the specific deuterium labeling at the carbon-2 atoms.

Rhodium(III)-Catalyzed Solvent Hydrogen Incorporation. The explanation of the above observations is clearly based upon incorporation of solvent hydrogen/deuterium at the carbon-1 atom of the alcohol produced. Whether this incorporation occurs during the catalytic reaction or is the result of a secondary reaction was further investigated by reacting the rhodium complex in deuterated solvent with an authentic sample of the alcohol formed but in the absence of the aldopentose substrate and the aldonolactone reaction product. To clarify further the reactivity, it was chosen to use the unsymmetrical arabinitol alcohol, which gives the possibility of distinguishing the individual resonances of all five carbon atoms. Figure 3 summarizes the results:

(A) Arabinitol is seen to be completely stable with respect to incorporation of solvent deuterium in acidic solution in the absence of rhodium complex.

(B) Addition of rhodium complex to arabinitol induces reactions which diminish the intensity of all of the original carbon resonances, except that of the carbon-3 atom. Simultaneously, new resonances at lower field appear. These resonances are attributed to two new singlets for carbon atoms 2 and 4, and two new triplets with components hidden under the original resonances for carbon atoms 1 and 5. This interpretation of the resonance pattern clearly demonstrates that solvent deuterium incorporation has occurred at the primary alcohol groups, that is, at carbon atoms 1 and 5, cf. the interpretation of the data in Figures 1 and 2.

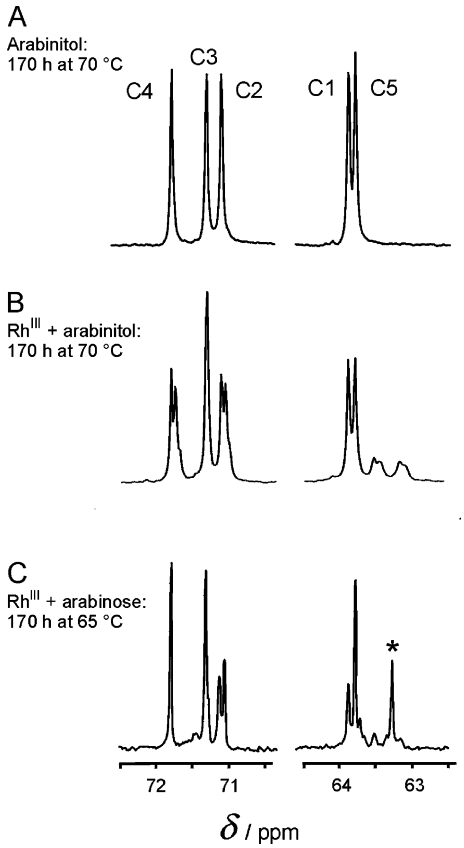


Figure 3. ^{13}C NMR spectra of arabinitol in the absence and in the presence of rhodium complex, and formed from arabinitol in the presence of rhodium complex. Resonance peak labeled "*" originates from parent arabinose substrate.

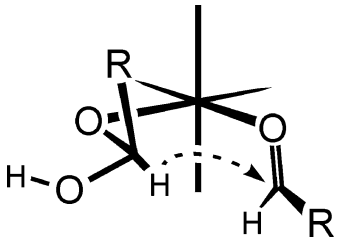
(C) The resonance pattern of arabinitol formed in deuterated solvent from arabinose, demonstrating that solvent deuterium has only been incorporated at carbon atom 1, as evidenced by the reduced intensity of the resonance of this carbon atom and the doubling of the carbon-2 resonance.

The spectral data in Figure 3 necessarily mean that the solvent deuterium incorporation has occurred while the substrate or the reaction product is coordinated to the metal atom during the catalytic cycle. The question of whether the incorporation could take place concomitant with the hydride transfer or is solely the result of a subsequent reaction of the coordinated alcohol prior to the aquation reaction is still unanswered, however. The latter possibility is clearly demonstrated to be operative and could well be the only mechanism.

Summary

cis-[Rh(cyc*b*)$(OH_2)_2]^{3+}$ catalyzes a disproportionation reaction between two aldopentose molecules, giving the corresponding alcohol and carboxylic acid, both with an unchanged configuration around carbon atoms 2, 3, and 4. The mechanism of this process may be envisaged as a hydride transfer from a coordinated hydrated aldopentose to a coordinated unhydrated aldopentose as shown in Scheme 3. This mechanism is analogous to that suggested for the classical Cannizzaro reaction,[9] which takes place in strongly basic solution. Under such conditions, the presently investigated carbohydrates would react to give undefined mixtures of polymeric substances.

Scheme 3



Two functions of the rhodium catalyst for the present reactions are consequently both to markedly enhance the acidity of one of the geminal hydroxy-groups of the hydrated carbohydrate and thereby promote the nucleophilicity of the geminal hydrogen atom, and simultaneously to activate a carbonyl carbon atom for such a nucleophilic attack.

One further comment is relevant in relation to the mechanism in Scheme 3, which is depicted with the two aldopentose substrates coordinated to the same rhodium center. Obviously the process could take place with the two substrates coordinated to different rhodium centers. Attempts mechanistically to distinguish these alternatives have not, however, been successful. The proximity of the reactants in the suggested reactive intermediate of Scheme 3 will, however, provide an attractive pathway for the reaction to take place.

Experimental Section

Chemicals. *cis*-[Rh(cyc*b*)$(OSO_2CF_3)_2](CF_3SO_3)$ was prepared according to the literature[7] and was used as the source of *cis*-[Rh(cyc*b*)$(OH_2)_2]^{3+}$ by dissolution in aqueous acid. The d-aldopentoses (Aldrich or Merck), D-[1-^{13}C]ribose and D-[2-^{13}C]ribose (Sigma), D-[1-^{2}H]ribose and D-[2-^{2}H]ribose (CIL), L-arabinitol, ribitol, and xylitol (Sigma), and D-Ribonic γ-lactone (Aldrich) were commercial products. The purity of the commercial substrates was confirmed by ^{1}H and ^{13}C NMR using 0.1 M solutions in aqueous 0.01 M $DClO_4$.

Aldose Reactions. Typically 150 μmol of aldose and 20 μmol of *cis*-[Rh(cyc*b*)$(OSO_2CF_3)_2]CF_3SO_3$ were dissolved in 600 μL of 0.010 M $DClO_4$ or $HClO_4$. This solution was used directly for the NMR measurements.

D-(2-^{13}C)Ribose Reaction. Here, 100 μmol of ^{13}C-labeled ribose and 20 μmol of *cis*-[Rh(cyc*b*)$(OSO_2CF_3)_2](CF_3SO_3)$ were dissolved in 600 μL of 0.010 M $DClO_4$. This solution was used directly for the NMR measurements, cf. Figure 2.

NMR Measurements. Proton decoupled ^{13}C NMR spectra were recorded at 62.896 MHz with a Bruker AC 250 MHz Fourier transform spectrometer. Data, typically about 3×10^4 transients, were recorded at 300 K using a pulse width of 2 μs (45°), a spectral width of 14 286 Hz, a relaxation delay of 0.5 s between pulses, and 32K data points giving a digitizer resolution of 0.872 Hz/point in the final spectrum. ^{1}H NMR spectra were recorded at 250.134 MHz using a pulse width of 4 μs (45°), a spectral width of 3703 Hz, and 32K data points giving a resolution of 0.226 Hz/point. Under these conditions, the acquisition times are 1.147 s (^{13}C) and 4.424 s (^{1}H) per free induction decay. A relaxation delay between pulses was not found to be necessary. ^{13}C DEPT spectra with $\tau =$ 3.8 ms and $\theta = 135°$ were used to achieve differentiation between CH and CH_2 groups. Chemical shifts are reported on the δ-scale

with reference to internal 1,4-dioxane at $\delta = 67.4$ ppm (^{13}C) and $\delta = 3.7$ ppm (^{1}H). For the reactions in nondeuterated solvents, an external 1,4-dioxane reference was used. Addition of base to the pentose solution causes polymerization, and apparently the polymers are sufficiently different to completely remove ^{13}C-resonances of unreacted pentose. This procedure was occasionally used to get more informative ^{13}C-spectra.

Acknowledgment. The Bruker NMR spectrometer was donated to the Royal Veterinary and Agricultural University by the Danish Department of Technology. This research has been supported by Statens naturvidenskabelige Forskningsråd through grant J.nr.11-7783.

IC0400989