

Mechanism of Metal Ion Catalyzed Carbohydrate Transformations. Stoichiometry of Aldopentose Rearrangement Processes Catalyzed by a Macrocyclic Chromium(III) Complex

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Eriksen, J., Mønsted, L. and Mønsted, O., 1995. Mechanism of Metal Ion Catalyzed Carbohydrate Transformations. Stoichiometry of Aldopentose Rearrangement Processes Catalyzed by a Macrocyclic Chromium(III) Complex. – Acta Chem. Scand. 49: 713–721 © Acta Chemica Scandinavica 1995.

The detailed stoichiometry of the reaction between the aldopentoses, ribose, arabinose, lyxose and xylose, and chromium(III) complexes of the optically active macrocyclic 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane tetraamine ligand, has been studied by a combination of ¹H- and ¹³C-NMR, of ion-exchange chromatography, and of deuterium and carbon-13 labelling. The reaction gives complexes of coordinated 2-hydroxycarboxylic acids by an intramolecular redox reaction, and the same reaction product ligand mixtures are obtained from all the pentoses, but with relative amounts which vary as a function of the temperature and the combination of chirality of chromium(III) complex and chirality of the carbon-4 atom of the aldopentose.

The suggested mechanism of this transformation process involves bidentate substrate coordination followed by protonation, dehydration, carbocation formation, deprotonation and formation of an enolic intermediate. The further reactions involve protonation followed by intramolecular 1,2-hydride shift, and deprotonation to give the coordinated deprotonated 2-hydroxycarboxylic acids. A parallel protonation of either the 4-hydroxy group or the carbon-3 atom of the enolic intermediate leads to the unsaturated 2,5-dihydroxypent-3-enoic acid or a diastereomeric mixture of the saturated 2,4,5-trihydroxypentanoic acids, respectively.

The mechanism established here for the chromium(III) catalyzed rearrangement process is discussed in relation to the molybdenum(VI) and nickel(II)-amine catalyzed epimerization processes at the carbon-2 atom of aldoses.

It was recently demonstrated that certain macrocyclic chromium(III) complexes induced 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.¹ The stoichiometry of these reactions was characterized in some detail and a mechanism was suggested which could also be valid for other metal ion initiated carbohydrate transformation processes. This type of reaction has apparently not been characterized previously,² and it was decided to investigate the possible transformation of other carbohydrates. The present work describes a stoichiometric study of aldopentose rearrangement processes catalyzed by the enantiomeric chromium(III) complexes of the optically active 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane, *cycb*, tetraamine ligand (Fig. 1 and Table 1).

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Table 1. Ligand and complex name abbreviations, cf. Fig. 1

<i>cycb</i>	5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane
<i>ss-cycb</i>	(7 <i>S</i> ,14 <i>S</i>)-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane
<i>rr-cycb</i>	(7 <i>R</i> ,n14 <i>R</i>)-5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane
<i>rr</i> -complex	<i>cis</i> -[Cr(<i>rr-cycb</i>)(OH) ₂](OH)] ²⁺
<i>ss</i> -complex	<i>cis</i> -[Cr(<i>ss-cycb</i>)(OH) ₂](OH)] ²⁺

Results and discussion

Reactivity. Red-violet dilute solutions of *cis*-[Cr(*cycb*)(OH)₂]³⁺ change colour to blue-violet after dissolution of a carbohydrate. At room temperature this transformation takes days for completion, but at 100 °C it is finished within a few minutes. Macroscopic ion-exchange chromatography of such solutions shows the presence of

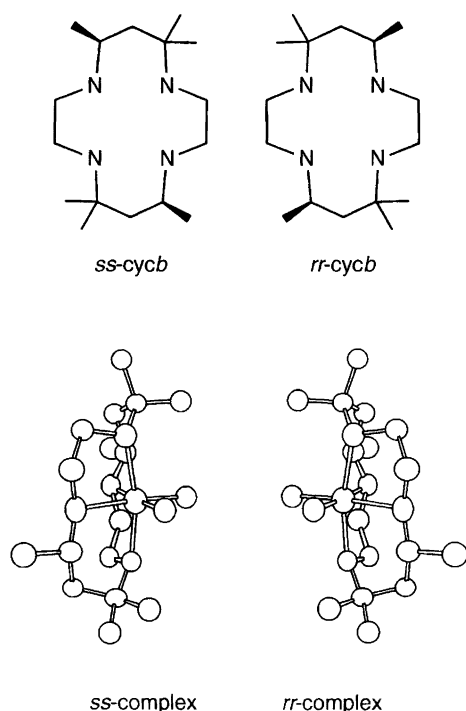


Fig. 1. (7*S*,14*S*)- and (7*R*,14*R*)-5,5,7,12,12,14-hexamethyl-1,4-8,11-tetraazacyclotetradecane and structure of the *cis*-chromium(III) complexes,¹ cf. Table 1.

components with charges of 1+ and 2+ in addition to the 3+ charged initial reactant as judged from the fractionation behaviour in dilute acidic solution. Solid crystalline products could not be obtained from these dilute solutions. In more concentrated solutions, however, solid brown products were formed, but these compounds contain only chromium(III) at the impurity level. The apparent amount of these latter products depended very much upon the identity of the carbohydrate, and seemed to be at a minimum for the aldopentoses. It was consequently decided to start the investigations using this series of carbohydrates.

Identification of chromium(III) complexes. Semiquantitative kinetic measurements in dilute acidic solutions indicate the deprotonated diaqua complex $cis-[Cr(cycb)(OH_2)(OH)]^{2+}$ to be the dominant chromium(III) reactant. In neutral and weakly acidic solutions this complex reacts with the aldopentoses shown in

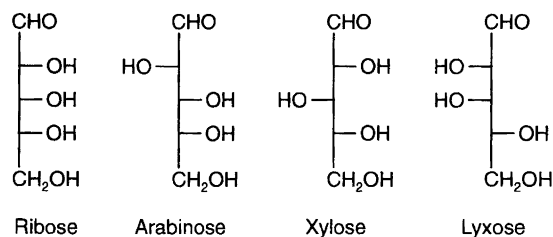


Fig. 2. Fischer projection of the four D-aldopentoses used in this work.

Fig. 2 to give products with spectral and acid-base properties characteristic for complexes of chelate deprotonated 2-hydroxycarboxylic acids. These products with a chelate ligand are formed initially, but at longer reaction times complexes coordinated with water and a monodentate carboxylate ligand are also present. These latter products appear to be formed by a secondary process involving partial aquation of the bidentate complex.

Spectral characteristics of the 1+ charged chelate complex vary as a function of the mode of preparation and purification, and a chromatographic analysis shows that the fraction of bidentate 2-hydroxycarboxylate complex contains at least four components. This is demonstrated in Fig. 3 for the product mixture formed from the enantiomeric $cis-[Cr(cycb)(OH_2)(OH)]^{2+}$ complexes and D-ribose.

Solid compounds could be isolated after chromatographic purification as perchlorate salts in low yields. Elemental analyses of such products gives C:Cr ratios of 21:1. This indicates the presence of one transformed aldopentose molecule in the chromium(III) complexes.

Reactivity comparisons of the substrate transformation reactions. Product mixtures containing four components characterized as complexes coordinated with a bidentate deprotonated 2-hydroxycarboxylic acid are formed from all the aldopentoses. It is further apparent that the product distribution among these four components in addition to being a function of temperature is a function of the combination of chirality of the chromium(III) complex and the chirality of the carbon-4 atom of the aldopentose, i.e. at a given temperature the same mixture of products are formed from one enantiomer of the chromium(III) complex and all the D-pentoses. This is further demonstrated by the comparisons of relative peak areas as shown in Fig. 4, which also indicate a parallel production of the four reaction products.

The detailed kinetics of the reactions have not been investigated in detail, but it is apparent from the data in Table 2 that the relative rates are dominated by the combination of chirality around the chromium(III) complex and the chirality around the carbon-2 atom of the aldopentose. For $cis-[Cr(ss-cycb)(OH_2)(OH)]^{2+}$ there is a preferential reactivity with the aldopentoses with an *R* configuration around the carbon-2 atom, i.e. $k(\text{D-arabinose}) < k(\text{D-ribose})$ and $k(\text{D-lyxose}) < k(\text{D-xylose})$. For $cis-[Cr(rr-cycb)(OH_2)(OH)]^{2+}$ the opposite relative rates are found. The remaining chiral centers of the aldopentose are seen to be less well defined as compared to the carbon-2 atom chirality.

A rationalization of these relative rates can be obtained if the rate-determining step for the transformations are supposed to involve an intermediate bidentate complex coordinated with hydroxy groups at carbon atoms 1 and 2 of the hydrated aldopentoses, a type of complex which has been isolated as an intermediate in the transformation of glyoxal into coordinated glycolate by the same chromium(III) complex.³ Figure 5 demonstrates the vari-

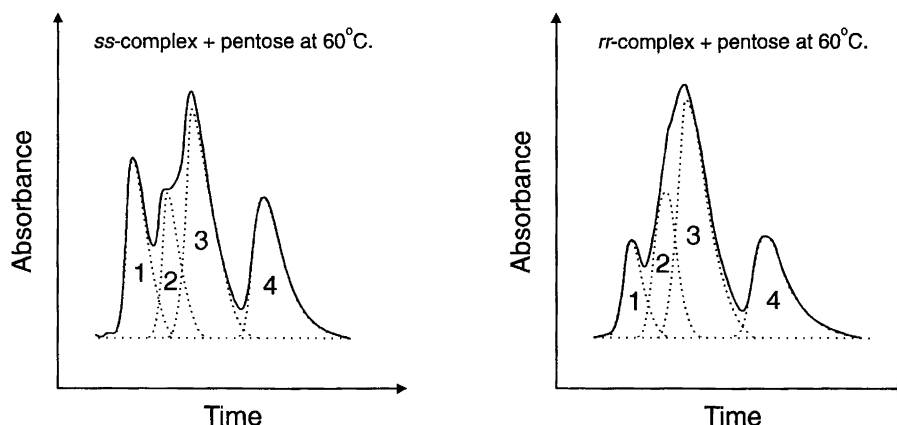


Fig. 3. Chromatographic fractionation of chelate 2-hydroxycarboxylate reaction products from D-ribose and *ss*-complex or *rr*-complex, respectively. Peaks 1 and 3 result from the diastereomeric complexes of the saturated 2,4,5-trihydroxypentanoic acids. Peaks 2 and 4 result from the diastereomeric complexes of the unsaturated 2,5-dihydroxypent-3-enoic acids (see text).

ous stereochemical possibilities for formation of intermediates for the present carbohydrate substrates, and it is seen that the higher relative rates are found for intermediates with supposedly less steric interaction between

methyl groups of the coordinated *cycb* ligand and substituents at the carbon-2 atom. This same type of interaction has previously been invoked to explain the relative formation rates of the diastereomeric lactate complexes.¹

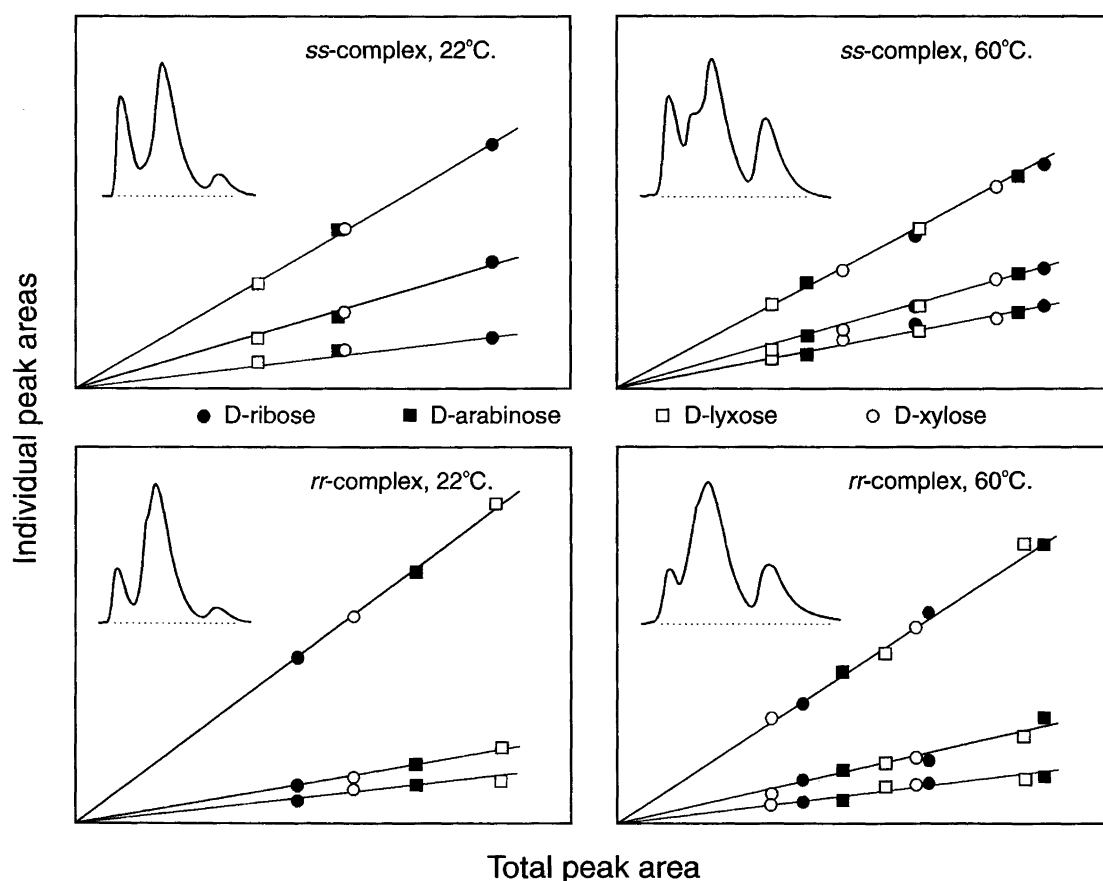


Fig. 4. Relative degrees of formation of chelate 2-hydroxycarboxylate complexes as function of temperature, of aldopentose and of chromium(III) complex chirality. The separation of peaks 2 and 3 was not well defined, cf. Fig. 3, and only the combined areas of peaks 2 and 3 are shown in the figure. The inserts show the chromatographic separation behaviour, cf. Fig. 3. Ordinate and abscissa units are identical.

Table 2. Pseudo-first-order rate constants, k , and rate constant ratios, for product formation in aqueous 0.010 M HBr solution with $C_{Cr} \approx 1.00$ mM and $C_{\text{pentose}} \approx 10.0$ mM.

Complex	$T/^\circ\text{C}$	k_r/s^{-1} (D-ribose)	k_a/s^{-1} (D-arabinose)	$k_r:k_a$	k_x/s^{-1} (D-xylose)	k_l/s^{-1} (D-lyxose)	$k_x:k_l$
ss-	60	5.1×10^{-4}	3.0×10^{-4}	1:0.59	3.2×10^{-4}	2.0×10^{-4}	1:0.62
ss-	22	2.1×10^{-6}	1.0×10^{-6}	1:0.46	1.0×10^{-6}	0.6×10^{-6}	1:0.60
rr-	60	2.5×10^{-4}	3.6×10^{-4}	0.70:1	2.3×10^{-4}	4.0×10^{-4}	0.58:1
rr-	22	0.7×10^{-6}	1.3×10^{-6}	0.54:1	1.0×10^{-6}	2.0×10^{-6}	0.49:1

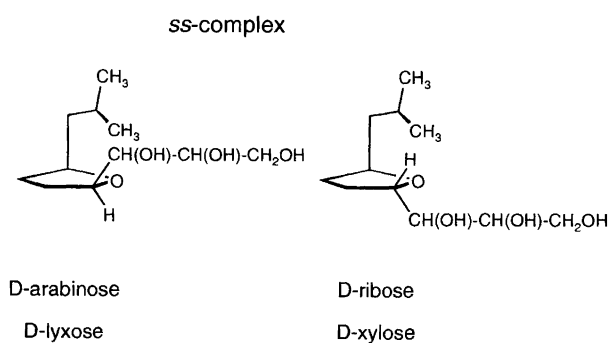


Fig. 5. Possible interactions between a methyl group of the *cycb* ligand and the substituents at the carbon-2 atom of the coordinated aldose, (see text).

Identification of reaction products. Further details of the substrate transformations were characterized by isolation of the 1+ charged chromium(III) containing reaction product mixtures formed in ordinary and in deuterated water. Decomposition of the isolated complexes in an acidic solution containing chloride and perchlorate ions gave solid *cis*-[Cr(*cycb*)Cl₂]ClO₄ and solutions which were sufficiently free of paramagnetic chromium(III) to be suitable for ¹H and ¹³C NMR measurements.

All ¹³C spectra of the products formed in H₂O show 25 resonances with identical positions independent of the identity of the aldopentose, of the chirality of the chromium(III) complex and of the temperature. The relative intensities, however, depend upon the temperature and the combination of complex chirality and chirality of the carbon-4 atom of the aldopentose, in agreement with the results of the chromatographic separations of the chromium(III) complex products, cf. Fig. 4.

The 25 resonances fall into groups of 5 and 20, respectively, and these two groups dominate spectra of products formed at high and low temperatures.

The five resonances in the ¹³C spectrum of the 'high-temperature' component are found in the ranges for carboxylic acid derivatives, unsaturated carbon atoms and carbon atoms bound to hydroxy groups. A DEPT spectrum further indicated the presence of one -CH=CH-unit, one -CH₂OH unit and one >CHOH unit. This assignment is supported by the coupling pattern in the ¹H-spectrum of the resonances due to the two hydrogen atoms bound to the unsaturated carbon atoms, which further indicates that these units are combined into a -CH(OH)-CH=CH-CH₂OH unit (Fig. 6). The coupling constant between the two hydrogen atoms is found to be

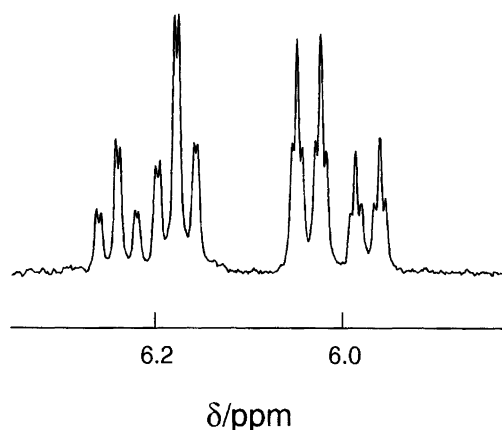


Fig. 6. ¹H NMR spectrum of the unsaturated 2,5-dihydroxypent-3-enoic acid in the region of the resonances of the hydrogen atoms at the double bond.

16 Hz, which indicates an *E*-configuration. Combination of these data with the properties of the chromium(III) reaction products and the mode of formation, as compared with that of the glyceraldehyde products, makes it likely that the liberated ligand is a mixture of the enantiomeric (*E*)-2,5-dihydroxypent-3-enoic acids, which on coordination to the chiral chromium(III) complex gives a mixture of diastereomeric complexes. Comparisons between the NMR spectrometric data and the chromatographic data make it further likely that these complexes are those eluted in peak numbers 2 and 4, cf. Figs. 3 and 4.

The 25 resonances in the ¹³C-spectrum of the reaction products in acidic solution are reduced to 15 resonances in basic solution. Acidification of such basic solutions re-establishes the original spectrum, but it is clear that the relative intensities vary immediately after the acidification: 10 resonances grow at the expense of 10 other resonances. This is demonstrated in the upper part of Fig. 7 for 4 of the 20 resonances of variable intensity. The five resonances of the 'high-temperature' unsaturated acid were not seen to vary in intensity by such a treatment.

Consideration of the positions of the 20 resonances in the ¹³C-spectrum of the 'low-temperature' components indicates the presence of four carboxylate units, four saturated carbon atoms and 12 carbon atoms with an attached hydroxy group. The DEPT spectra further identify these latter 16 carbon atoms as four >CH₂ units, four-CH₂OH units and eight >CHOH units. A comparison with previous results for the chromium(III)-induced gly-

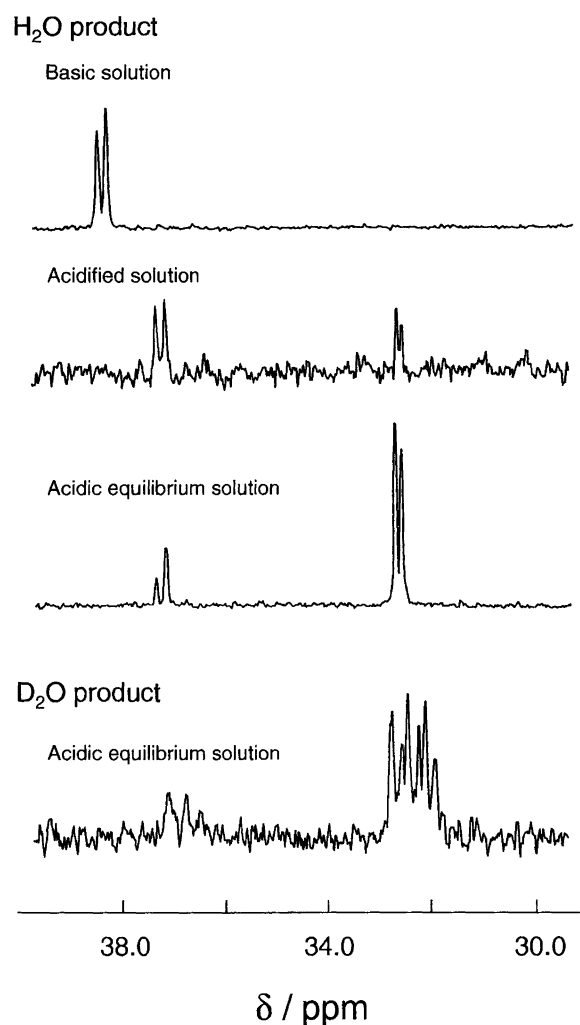


Fig. 7. ^{13}C NMR spectra of reaction products formed in H_2O and D_2O in the region of $>\text{CH}_2$ and $>\text{CHD}$ carbon atom resonances (see text).

eraldehyde transformations makes it likely that this product mixture contains the diastereomeric 2,4,5-trihydroxypentanoic acids. In acidic solution these acids are in slow equilibrium with the corresponding lactones. In basic solution the lactones are hydrolyzed and the acid deprotonated to give a mixture of the two diastereomeric carboxylate anions. By coordination to the chiral macrocyclic chromium(III) complex each enantiomer of the complex gives a mixture of two diastereomers. These cations are seen as peak numbers 1 and 3 at the chromatographic separations for both enantiomers, cf. Figs. 3 and 4. The racemic chromium(III) complex will give a mixture of four diastereomers, which, however, cannot all be expected to be separated, cf. the separation behaviour shown in Fig. 3.

The dominating lactone formation for these acids further supports the evidence of an *E*-configuration of the unsaturated acid, as the *Z*-configuration would be expected to give a lactone formation analogous to that seen for the saturated acids.

The ^{13}C NMR spectra of products prepared in D_2O are identical to those prepared in ordinary water, except for the resonances in the range of saturated carbon atoms as shown in the lower part of Fig. 7. These spectra show unambiguously incorporation of *one* deuterium atom from the solvent water into the methylene group of the saturated acid lactones. Minor amounts of the undeuterated forms are probably also present. These latter products are most likely the result of the decrease in isotopic purity of the solvent water caused by the dissolution of undeuterated reactants.

The ^{13}C NMR spectrum of the unsaturated acid does not show any signs of deuterium incorporation. A characteristic of the reactions in D_2O , however, is the formation of a significantly higher proportion of the unsaturated acid.

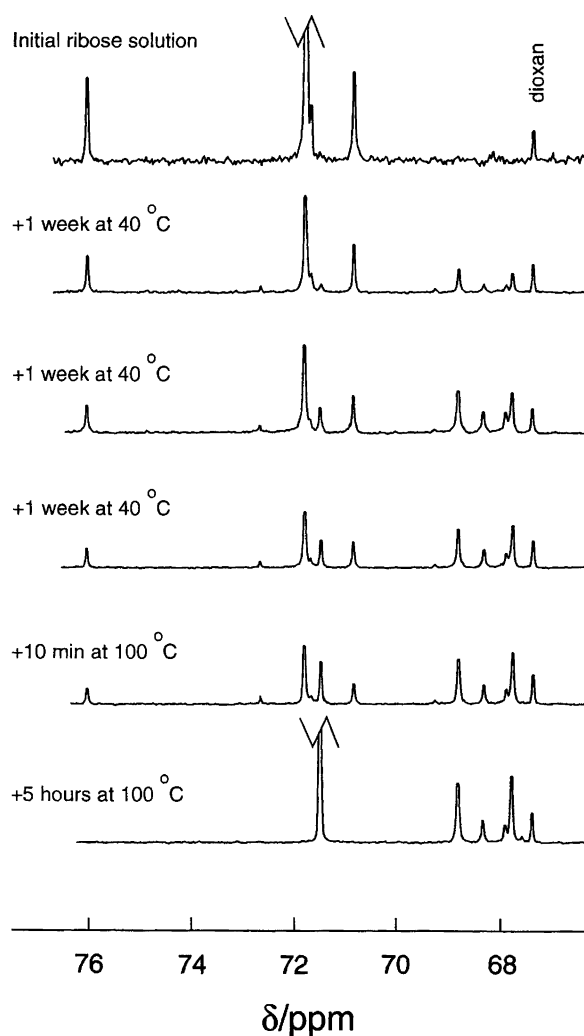


Fig. 8. ^{13}C NMR spectra of reaction mixtures of D -(2- ^{13}C)-ribose and $\text{cis-}[\text{Cr}(\text{cycb})(\text{OH}_2)(\text{OH})]^{2+}$. Only resonances due to the labelled ^{13}C atom are visible. The four ribose peaks are those corresponding to the α - and β -furanose and pyranose forms. The peak at $\delta=71.4$ originates from the unsaturated acid, and the four peaks in the range $67.5 < \delta < 69$ are from the saturated acids and lactones.

Disappearance of D-ribose and formation of the uncoordinated carboxylic acids could be monitored directly using D-(2- ^{13}C)-ribose. This is demonstrated in Fig. 8, which shows a parallel production of the three carboxylic acids and two lactones. The preferred formation of the unsaturated acid at higher temperatures is also apparent.

The lack of the pure diastereomeric reaction products has prevented an accurate characterization of the diastereomer formation ratios. If comparisons with other diastereomeric 2-hydroxycarboxylate complexes of the Cr(cycb)-unit are valid with respect to elution behaviour and molar absorption coefficients at the chromatographic detection wavelength, then the formation of diastereomers follows the pattern earlier established for formation of the diastereomeric lactate complexes. This is being investigated further.

Mechanism of aldopentose rearrangement processes. The mechanism of formation of the various coordinated 2-

hydroxycarboxylates arrived at on the basis of the above experiments is given in Fig. 9. The initial stages in this mechanism are analogous to those proposed for formation of coordinated lactate from glyceraldehyde, involving chelate substrate binding, and hydrogen ion catalyzed enol formation as the first essential steps. Additional evidence in favour of a chelate coordination comes from the inability to detect a similar reactivity between the chromium(III) complex and 2-deoxyribose. The original chirality of carbon atoms 2 and 3 has been lost in this suggested intermediate of a coordinated enol, which explains that the reaction product mixture is only a function of the chirality of the carbon-4 atom.

The enolic intermediate is a diastereomeric mixture of cations with an opposite carbon-1 atom chirality. Different relative amounts of these diastereomers are possible as a function of the original aldopentose identity. Apparently, however, these differences are either too small to be seen, or the lifetime of the diastereomeric intermediate is

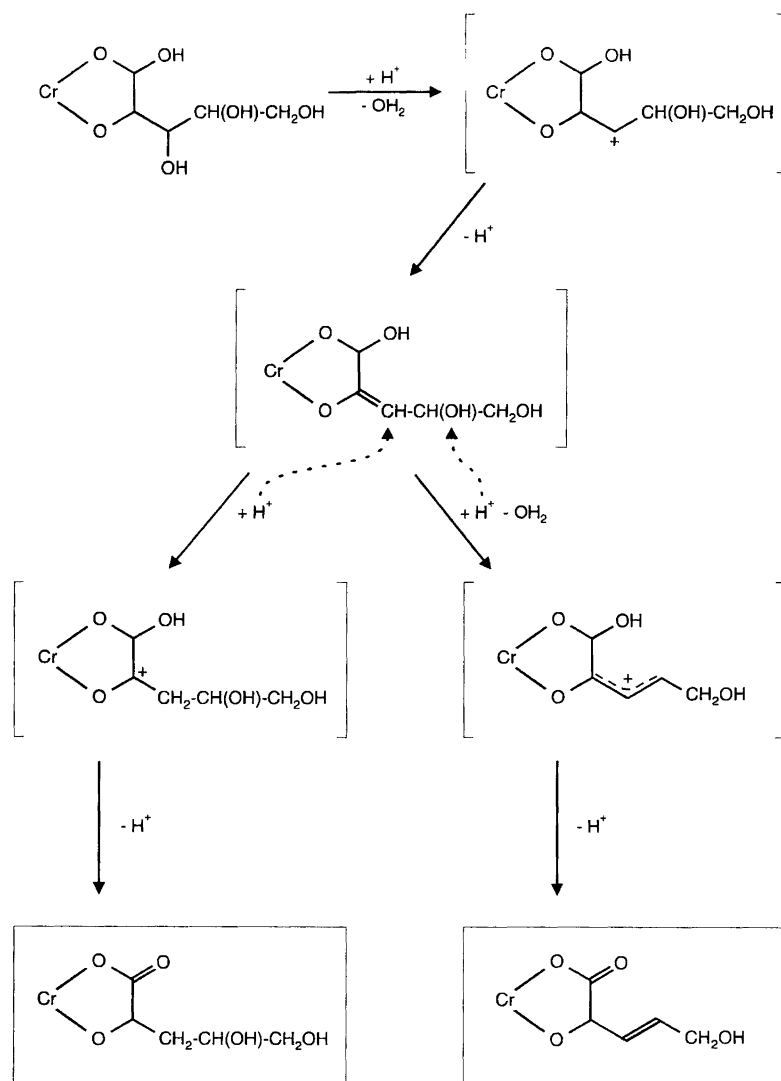


Fig. 9. Suggested mechanism of aldopentose transformations catalyzed by $\text{cis-}[\text{Cr}(\text{cycb})(\text{OH}_2)(\text{OH})]^{2+}$.

sufficiently long as compared to the equilibration time for the racemization process around the carbon-1 atom for the same diastereomer mixture of the intermediate to be obtained for all the different aldopentoses.

The further reactions of this intermediate involve hydrogen ion incorporation from the solvent to give different carbocations responsible for the formation of the unsaturated and the saturated acids, respectively. The sites of protonation of the enolic intermediate are markedly different for these two carbocations to be formed. Formation of the unsaturated acid is the result of protonation at the hydroxy group of the carbon-4 atom followed by dehydration, 1,2-hydride shift and deprotonation. Formation of the saturated acid, however, is the result of protonation of the carbon-3 atom again followed by 1,2-hydride shift and deprotonation. These parallel reactions explain that solvent hydrogen is incorporated into only the saturated acid and at the carbon-3 atom, and also explains the possibility of different relative amounts of unsaturated and saturated acids in H_2O vs. D_2O and at different temperatures.

The unsaturated acid appears to be formed stereospecifically, and the presently available evidence points towards an *E* form. The specificity is evidently a function of the structure of the enolic intermediate. The possible isomers of this intermediate and the further intermediates are shown in Fig. 10. Probably, intermediates leading to *Z* isomers are sterically too crowded to play any significant role in the reactivity.

Molybdenum(VI)⁴ and selected nickel(II) amine complexes⁵ have earlier been demonstrated to cause epimerization at the carbon-2 atom of aldoses, as the result of an interchange of carbon atoms 1 and 2. Such a process has not been demonstrated to play any detectable role for the present macrocyclic chromium(III) complexes. Possible reasons for this different behaviour are demonstrated in Fig. 11, which shows a proposal for the mechanism of the carbon-2 epimerization process. Key features in this mechanistic scheme, different from that of the chromium(III) catalyzed aldopentose rearrangements, are coordination of the aldehydic form of the carbohydrate substrate and formation of a carbocation stabilized in part by the hydroxy group at the carbon-3 atom. Steric hindrance from the two protruding methyl groups of the *cycb* ligand, cf. Fig. 1, will probably prevent the formation of such carbocations for the present chromium(III) complexes, and coordination of the aldehydic substrate in the hydrated form is probably a prerequisite for the easy formation of the coordinated carboxylates.^{1,3}

Experimental

Caution. The perchlorate salts described here are potentially explosive and should be handled accordingly.

Chemicals. *cis*-[Cr(*cycb*)(OH)₂]₂Br₃·aq, *cis*-[Cr(*cycb*)Cl₂]₂Cl, *cis*-[Cr(*ss-cycb*)Cl₂]₂ClO₄ and *cis*-[Cr(*rr-cycb*)Cl₂]₂ClO₄ were prepared by available methods.^{6,7}

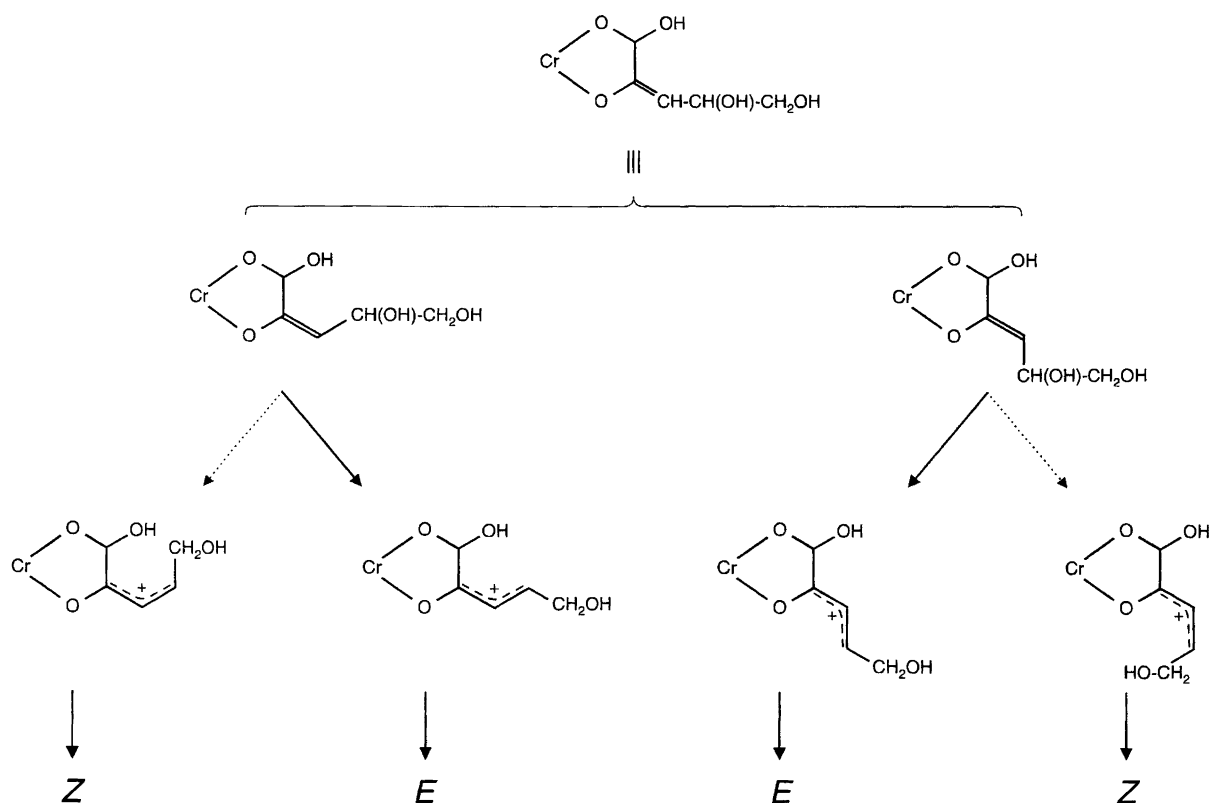


Fig. 10. Suggested detailed mechanism for the stereospecific formation of the (*E*)-2,5-dihydroxypent-3-enoic acid.

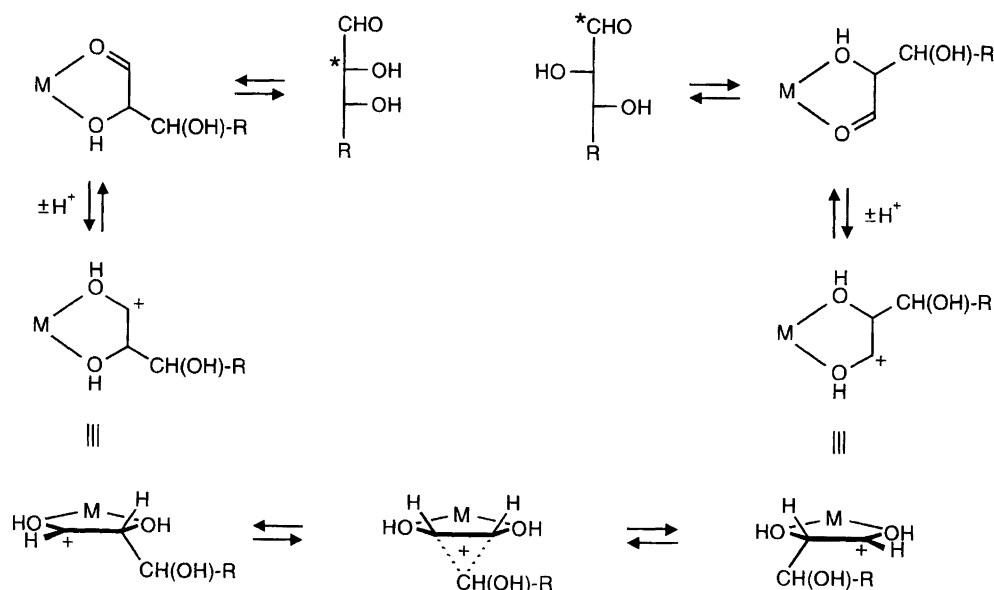


Fig. 11. Suggested mechanism for the molybdenum(VI) and nickel(III) amine catalyzed carbon-2 epimerization process.

The D-aldopentoses, L-arabinose and L-xylose (Aldrich or Merck), D-(2- ^{13}C)ribose (Aldrich) and 2-deoxy-D-ribose (Fluka) were commercial products. Sodium bromide and aqueous hydrogen bromide were the best available commercial grades, which were purified as necessary: $\text{NaBr}\cdot 2\text{H}_2\text{O}$ was recrystallized from water. $\text{HBr}(47,\text{aq})$ was distilled from metallic tin. The purity of the commercial substrates was controlled by ^1H and ^{13}C NMR using 0.1 M solutions in aqueous 0.01 M DClO_4 .

Stoichiometric studies. Product formation was investigated by reacting the enantiomeric chromium(III) complexes with the aldopentose substrates in 0.010 M aqueous hydrogen bromide solution. The product formation was monitored by FPLC-chromatography using a Pharmacia FPLC apparatus equipped with a Mono S HR 5/5 column. Gradient elution from aqueous 0.010 M HBr to aqueous 0.010 M HBr + 0.20 M NaBr were used for separating the chelate hydroxycarboxylate complexes, cf. Fig. 3 and the data in Table 2. Unreacted chromium complex was removed with 0.010 M HBr + 1.0 M NaBr .

Isolation of 2-hydroxycarboxylic acid reaction products. Solutions of the transformed aldopentose reaction products for the NMR measurements were made by reacting 0.4 mmol of chromium(III) complex with 1.6 mmol substrate in 10 ml D_2O or H_2O at 40°C for two days. The reaction product complexes were isolated by ion-exchange chromatography using SP Sephadex C-25 by elution with 0.25 M NaCl . The fraction containing chelate 2-hydroxycarboxylate complexes was evaporated to dryness at 40°C . The chromium(III) complexes were extracted with ethanol and filtered from undissolved NaCl . The ethanolic solution was evaporated to dryness, treated with 1 ml D_2O and again evaporated to dryness. The resulting solid was reacted with 1.0 ml 1 M DClO_4 +

150 mg NaCl at 100°C until an almost colourless solution and a precipitate of *cis*- $[\text{Cr}(\text{cycb})\text{Cl}_2]\text{ClO}_4$ had formed. The precipitate was removed by filtration, and the resulting solution was used for the NMR measurements.

D-(2- ^{13}C)ribose reaction. 49 μmol ^{13}C -labelled ribose and 18 μmol *cis*- $[\text{Cr}(\text{cycb})(\text{OH})_2]\text{Br}_3\cdot 2\text{aq}$ were dissolved in 0.6 ml 0.010 M DClO_4 . This solution was used directly for the NMR measurements, cf. Fig. 8.

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°), spectral width 14286 Hz, and 32K data points giving a digitizer resolution of 0.872 Hz per point in the final spectrum. ^1H 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 per point. Under these conditions the acquisition times are 1.147 s (^{13}C) and 4.424 s (^1H) per free induction decay, and a relaxation delay between pulses was not found to be necessary. ^{13}C DEPT spectra⁸ with $\tau = 3.8$ ms and $\theta = 135^\circ$ 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 (^1H).

Acknowledgements. The Perkin-Elmer Lambda 17 spectrophotometer and the Pharmacia FPLC-equipment were obtained by grants from *Statens naturvidenskabelige Forskningsråd* to Dr. P. Andersen (J.nr. 11-5962) and Dr. A. Hammershøi (J.nr. 11-6964). The Bruker NMR spectrometer was donated to the Royal Veterinary and Ag-

ricultural University by the Danish Department of Technology. This research has been supported by *Statens naturvidenskabelige Forskningsråd* through grant J.nr. 11-7783.

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Received January 20, 1995.