Rearrangement of the Carbon Skeleton of Aldoses is catalysed by Nickel(II) Complexes

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Carbon-13 n.m.r. studies utilizing [1-^{13}C]-D-glucose demonstrate that the apparent C-2 epimerization catalysed by $[Ni(H_2O)_2(tmen)_2]Cl_2$ (tmen = *N,N,N'*-trimethylethylenediamine) in fact proceeds *via* a molecular rearrangement in which the C-1 carbon label is found at the C-2 position of the product mannose.

In 1982 Barker and co-workers demonstrated using carbon-13 labelling techniques that the apparent epimerization reaction of aldoses which is catalysed by molybdate ion[1] in fact involves a rearrangement of the carbon skeleton.[2] This remarkable reaction is so unexpected that no mechanistic insights beyond the initial observations have been forthcoming. Recently Tanase *et al.*[3] have noted that C-2 epimerization of aldoses can be catalysed by nickel(II) complexes of *N,N,N'*-trimethylethylenediamine (tmen). Several observations indicate that this epimerization differs significantly from the familiar base catalysed aldose–ketose isomerization.[3] Alternatively, the involvement of a metal chelate suggests an analogy to the Barker rearrangement.

The possibility of a skeletal rearrangement can be readily tested by the use of a [1-^{13}C] carbohydrate.[2] A study was carried out in CD_3OD utilizing [1-^{13}C]glucose and 0.50 equiv. of $[Ni(H_2O)_2(tmen)_2]Cl_2$. Initial proton decoupled ^{13}C n.m.r. spectra show the expected two resonances arising from the α- and β-anomers of the D-glucose. Even at an ambient probe temperature of 21 °C small resonances near δ 71 became visible, and these increase rapidly upon heating the mixture to 60 °C as described by Tanase *et al.*[3] Hydrolysis of the nickel(II) complex as described in ref. 3 yields the products corresponding to the spectrum shown in Figure 1(B) which, based on the known ^{13}C carbohydrate shifts,[4] can immediately be assigned to the C-2 resonances of α- and β-D-mannose. Hence, the nickel(II) complex catalyses reaction (1).

$$[1\text{-}^{13}C]\text{-D-glucose} \xrightarrow{[Ni(H_2O)_2(tmen)_2]Cl_2} [2\text{-}^{13}C]\text{-D-mannose} \quad (1)$$

These results demonstrate unequivocally that the epimerization noted by Tanase *et al.*[3] in fact proceeds *via* a skeletal rearrangement which is analogous to that catalysed by the

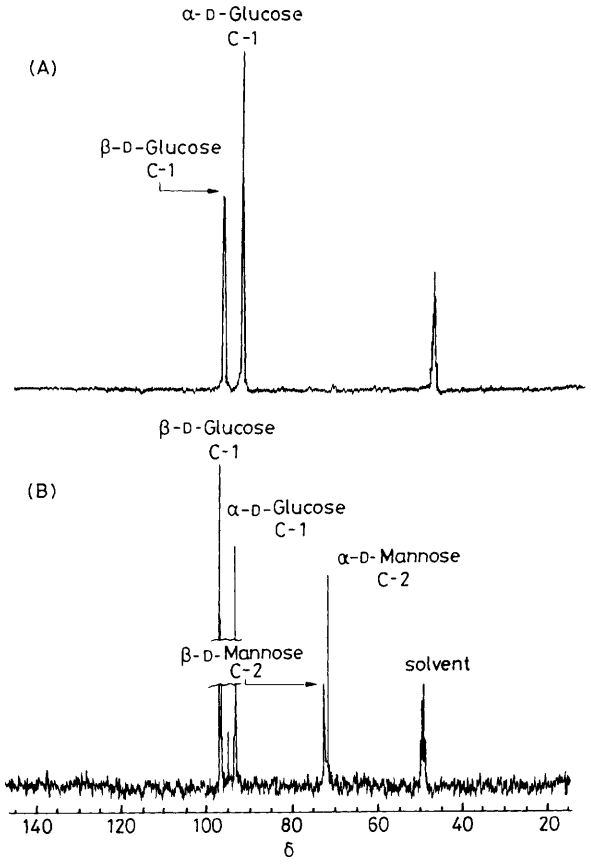

Figure 1. (A): Proton decoupled ^{13}C n.m.r. spectrum, obtained at 90 MHz on a Nicolet NT-360 spectrometer, of 0.1 M [1-^{13}C]-D-glucose mixed with 0.05 M $[Ni(H_2O)_2(tmen)_2]Cl_2$ in CD_3OD showing the two ^{13}C resonances arising from C-1 of α- and β-D-glucose. Spectrum corresponds to 64 pulses. (B): Proton decoupled ^{13}C n.m.r. spectrum of mixture (A) after heating for 3 min at 60 °C, dissolution in H_2O, and neutralization with sulphuric acid as described by Tanase *et al.*[3] Spectrum corresponds to 1401 transients. Chemical shifts are relative to external $SiMe_4$. The solvent CD_3OD resonance is at δ 49.3.

molybdate ion.[2] This mechanism can presumably be extended to cover the present situation. The direct involvement of the hydrated form of the aldehyde rather than the free aldehyde species could be accommodated within the context of a pinacol type rearrangement.[5] A further possibility involves a direct adduct of the tmen to form a carbinolamine intermediate as proposed by Tanase *et al.*[6]

One of the more remarkable aspects of the nickel(II) catalysed rearrangement is the extremely mild set of conditions required for reaction; measurable rearrangement occurs at the ambient n.m.r. probe temperature of 21 °C. The fact that, in contrast with the molybdate catalysed rearrangement, such structural rearrangements can occur under such mild conditions suggests that analogous processes might occur in biological systems. Although nickel(II) is not commonly found in such systems, other more prevalant metals might also be active.

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