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Note

A short note on the epimerization of aldoses [1]

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Abstract

It is postulated that, in the epimerization of glucose in alkaline solution catalysed by Ca^{2+} ions (and other cations of similar size), the intermediate is a complex of the cation with O-1, O-2, O-3 and O-4 of the sugar and that the reaction proceeds, like the Bílik reaction, with rearrangement of the carbon chain. © 1997 Elsevier Science Ltd.

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The classical method for the epimerization of aldoses at C-2 – with bases, usually sodium hydroxide – is the Lobry de Bruyn–Alberda van Ekenstein transformation (LdB–AvE) which has been extensively studied [2]. Its major disadvantage is that it tends to yield more of the ketose than of the epimeric aldose. However, Kusin [3] found that when glucose was treated with 1 equivalent of calcium hydroxide in aqueous solution at ambient temperature, mannose was formed but not fructose; treatment with sodium hydroxide under the same conditions gave much fructose and little mannose. This claim was not supported by other workers ([2], pp 81–82) but they used much less calcium hydroxide, sufficient only to give the high pH required for the transformation; Kusin's work has been largely forgotten. Quite recently, however, the calcium-catalysed epimerization has been rediscovered [4]; it shows some curious features which will be discussed in this Note.

Aldoses can be epimerized at C-2 by other methods, none of which produces a ketose. One is by the reaction named after its discoverer, Bílik [5,6]: treatment with catalytic amounts of molybdic acid will epimerize aldoses to a thermodynamic equilibrium mixture of the two epimers. Another method, studied by Yoshikawa and coworkers [7], uses complexes of Ni^{2+} and a diamine as the catalyst. When they employed Ca^{2+} instead of Ni^{2+}, the reaction still proceeded [8] – surprisingly, because calcium ions do not form complexes with diamines. Subsequently it was found that, even in the absence of a diamine, Ca^{2+} will catalyse epimerizations in alkaline solution [4], thus confirming Kusin's observations; one or more equivalents of calcium were used in these experiments.

These three methods of epimerization were found to differ fundamentally from the LdB–AvE transformation [7–9]. Whereas the latter proceeds through an enediol, the other three methods involve a 1,2-shift of the carbon skeleton whereby the bond from C-3 migrates from C-2 to C-1. The shift is stereospecific, the former C-1 becoming the new C-2 with inverted configuration. Such a 1,2-shift needs a rigid framework which holds the atoms in the required conformation; such rigidity is achieved by complex formation.

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[1] Complexes of Carbohydrates with Metal Cations, Part 18. For Part 17, see ref. [1].

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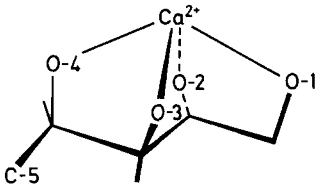

One puzzling feature of this reaction is that it was claimed to be specific for calcium ions. Since it is carried out in alkaline solution, the LdB–AvE reaction will occur concurrently, but if the rate of the former is much higher, little fructose will be produced. Strontium ions also catalyse the epimerization but to a lesser extent, and much fructose is formed; the other nine cations tested by the Japanese workers [4] proved ineffective.

Calcium ions complex readily with polyols; lanthanum ions complex even better [10]. We found that under the standard conditions used by the Japanese workers, lanthanum catalysis produced approx. the same amount of mannose as did calcium. However, lanthanum is less suitable than calcium for this epimerization because lanthanum hydroxide is a weak base; addition of only one equiv of sodium hydroxide to a lanthanum acetate solution gives a pH of less than 9, lower than required for the epimerization [4]. Nevertheless, 29% of mannose was found to be formed in methanolic solution; much less in water. When 3 equiv. of sodium hydroxide were added, the solution became strongly alkaline but the amount of mannose produced was about the same (26% in methanol, 28% in water). However, by then most of the lanthanum had precipitated as its hydroxide.

Neodymium (which forms stronger complexes with alditol than does lanthanum [1]) as a catalyst provided a clean result: 80% of glucose and 20% of mannose were found but no fructose could be detected in the ^{13}C NMR spectrum. Europium proved to be a disappointment: 70% glucose, 15% mannose, 15% fructose. Europium hydroxide has a lower solubility than lanthanum or neodymium hydroxide; apparently there are insufficient europium ions in alkaline solution to function as catalyst. LdB and AvE have claimed [11] that no fructose was formed when the epimerization was conducted with lead hydroxide; we could not confirm this. In fact, we found that more fructose was formed than mannose.

Clearly, there are several cations which catalyse the epimerization but, for practical purposes, calcium is the best because it is readily available and its hydroxide has sufficient solubility.

The advantage of catalysis by cations is that the proportion of mannose to glucose can be increased much above that in the thermodynamic equilibrium (28:72). Cations complex better with mannose than with glucose [10], and by using an excess of calcium in ethanolic solution, the yield of mannose can thus be increased to over 50%. It appeared that this would be an excellent method for producing L-ribose from L-arabinose. However, it was found that in this case no epimerization occurred; under the usual conditions of the reaction, ribulose and another compound (probably an acid) were formed but no ribose. It had already been shown that the epimerization by the calcium–diamine system did not proceed with galactose, talose, arabinose or ribose [8] and we confirmed that this was also the case with calcium hydroxide alone. We also found that allose did not give altrose. The gulose–idose pair was not tested because of the extreme lability of idose to high pH's.

It appears therefore that this epimerization applies only to the glucose–mannose (and the xylose–lyxose) system; a *threo* configuration at C-3 and C-4 is required. The other methods of epimerization apply to all aldoses. Yanagihara et al. [4] have postulated an intermediate complex with the calcium ion being bonded to O-1, O-2 and O-3; this would not explain the steric requirements of the reaction. It is now suggested that the intermediate complex has the structure shown as **1**, with the cation complexed to four oxygen atoms of the acyclic form of the sugar; the distribution of the negative charge and of the hydroxylic hydrogen atoms is uncertain and is not indicated. The complex does not contain the enediol structure; when the epimerization of mannose was carried out in deuterium oxide, no deuterium was incorporated into the glucose formed, as shown by its ^{13}C NMR spectrum. In the LdB–AvE transformation, which proceeds mainly through the enediol, extensive deuteration of the product occurs [12]. The enediol is less suitable for quadridentate complex formation, owing to the rigidity of the C-1–C-2 bond. It appears from Kusin's work [3] that the calcium ion not only catalyses epimerization but also suppresses the formation of fructose, probably by tying up the glucose as a complex.

If the sugar has a *threo* configuration at C-3 and C-4, complexing as shown in **1** is readily achieved; however, if C-3 and C-4 are *erythro*, C-5 would be close to O-2 and the conformation of the complex would be unfavourable. Cations usually complex with only three oxygen atoms of alditols [10]; however, in this case, being in alkaline solution, the sugar will be present as an anion, and that may explain the four-fold coordination. Barker and coworkers [9] postulated a molybdate complex involving four oxygen atoms as the intermediate in the Bílik reaction; however, the molybdate ion is binuclear and much larger than the calcium cation; both metal atoms are involved in the formation of a complex and there is no hindrance to complex formation regardless of configuration at C-4.

To test this suggestion, the reaction was carried out with 4-deoxy-D-glucose (4-deoxy-D-*xylo*-hexose); no epimerization was observed. It was also carried out with 4-*O*-methyl-D-mannose; epimerization occurred but at a slower rate than with mannose (13% epimerized in 5 min in aqueous solution, compared to 20% of mannose [4]). The methoxy group forms weaker complexes than a hydroxy group [10].

In order to bridge the four oxygen atoms without serious distortions, an optimum ionic radius is required; Ca^{2+} and La^{3+} seem to have such a radius (0.99 and 1.05 Å; the best radius for complexing with alditols is 0.95–0.98 Å [1]). Sr^{2+} and Pb^{2+} are somewhat larger than ideal, and Ba^{2+} is too large to be effective. Cations which are much smaller than Ca^{2+} do not complex well with polyols [10].

Being restricted to glucose and mannose, and their derivatives, the epimerization with calcium hydroxide is not particularly useful because these compounds are readily available. Maybe it would be useful for the preparation of isotopically labelled mannoses because of the better yield obtained, compared with other methods; or for the preparation of L-mannose. However, the reaction is of interest because the carbon–carbon migration occurs with such ease (10 min at 65° is sufficient to almost reach equilibrium; the Bílik reaction requires 4 h at 90°), and a detailed study of its mechanism would be of interest.

Experimental

Epimerizations were conducted under the standard conditions of Yanagahira et al. [4]: 5 min at 65°C. The products were analysed by HPLC, using a Waters Radial-Pak column (10 × 0.8 cm) of amino-propyl-bonded silica with acetonitrile–water (7:3) as the mobile phase; flow rate was 2.0 mL per minute. Some of the products were analysed by ^{13}C NMR spectroscopy.

With 1 eq of NaOH, lanthanum acetate gave only small amounts of other sugars; with 2 eq, it gave glucose:mannose:fructose in the ratio 88:9:3; with 3 eq, 67:28:5 which changed to 65:30:5 after 10 min and to 48:21:24 after 20 min; by that time the LdB–AvE reaction proceeded too far. For the reaction in methanol, lanthanum chloride was used instead of the acetate, which is not soluble in methanol. With 1 eq of NaOH, the ratio was 64:26:10; with 2 eq, 56:29:15. Other results are given in the text.Thanks are due to Professor J.D. Stevens for a gift of 4-*O*-methyl-D-mannose and to Dr C.P.J. Glaudemans for a gift of methyl 2,3-di-*O*-benzoyl-4-deoxy-α-D-glucopyranoside (from which 4-deoxy-D-glucose was prepared).

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