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THE "FORMOIN REACTION" : A PROMISING ENTRY TO CARBOHYDRATES FROM FORMALDEHYDE

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Summary: Formaldehyde condensation catalyzed by the conjugate bases of thiazolium ions, leads to a complex mixture ("formoin mixture") of unbranched aldoses and ketoses, in which glucose, galactose, glyceraldehyde dimer, xylose and arabinose have been identified.

Since Butlerow first reports[1] in 1861 on the alkali (calcium hydroxide) catalyzed autocondensation of formaldehyde to a complex carbohydrate mixture, the formose reaction (a loose denomination which includes Butlerow reaction itself and other rather closely related modifications) has been of interest in relation with such important subjects as photosynthesis, primordial origin of monosaccharides, industrial manufacture of edible carbohydrates and continuous recycling of metabolic CO_2 and H_2O during sustained space flight[2]. However, actual knowledge on formose reactions points to an unescapable conclusion: formation of branched-chain sugar and sugar-alcohols (which are toxic substances) is one of the dominant and unavoidable processes that take part in this very complex reaction[3]; consequently, if the final goal is the synthesis of edible, normal-chain sugars, a new approach to the autocondensation of formaldehyde should be looked for.

It is known[4] that the benzoin condensation, which is limited to aromatic aldehydes when cyanide is the catalyst, can be extended to aliphatic aldehydes if a conjugate base of a thiazolium ion is used instead, but, to our knowledge, no report on the "benzoin condensation" of formaldehyde has been published.

We have found now that under the catalytic action of a conjugate base of a thiazolium ion (specifically, that of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium ion or of thiamine), formaldehyde enters in a rather complex reaction that, noting the way in which the first reaction product is formed (see below), we call provisionally the "formoin reaction".

A typical experiment is as follows: Paraformaldehyde (40.0 g; 1.33 mol) is added, under continuous stirring, to a solution of triethylamine (18.8 g; 186 mmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (12.5 g; 185 mmol)[a,b] in DMF (250 ml) at 100ºC[c,d]; after 30 min at this temperature, more paraformaldehyde (10.0 g; 330 mmol) is added and, in a similar way, addition of formaldehyde is repeated twice more[e,f]. After neutralization with conc. HCl, DMF is vacuum distilled, the resulting oil is poured into water and the water solution is submitted for 12 h to continuous extraction with ether. The washed water solution is treated (3 times) with active charcoal and passed until neutral pH through deionizing columns (30x3 cm) Kastel A300 (OH^-) and Kastel C300 (H^+) (at least three passages are necessary). Removing of water affords a very viscous oil (15 g) of a yellow or reddish colour.

Notes. a) Thiamine has also been used successfully as catalyst. b) Experiments employing ten times less catalyst were satisfactory. c) The reaction can be conducted at lower temperatures and it takes place even at room temperature. d) Solution of formaldehyde is practically instantaneous, whereas in the absence of catalyst no solution is observed. e) Addition of formaldehyde can be repeated as many times as desired, until no more solution is observed (thiazolium rings are not undefinitely stable). f) Reaction progress was monitored by g.l.c. chromatography of samples prepared by mixing aliquots (0.5 ml) with anhydrous pyridine (0.5 ml), hexamethyldisilazane (0.4 ml) and trimethylchlorosilane (0.2)[5].

Some of the more significant experimental results, based on g.l.c./m.s. studies, are the following:

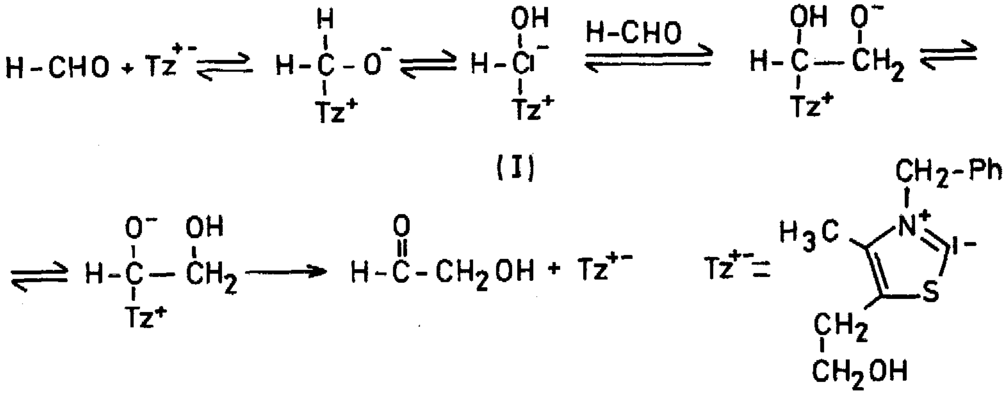
a) At 100ºC, reaction times up to 15 min, lead to a very simple mixtures in which the main component is glyceraldehyde dimer.

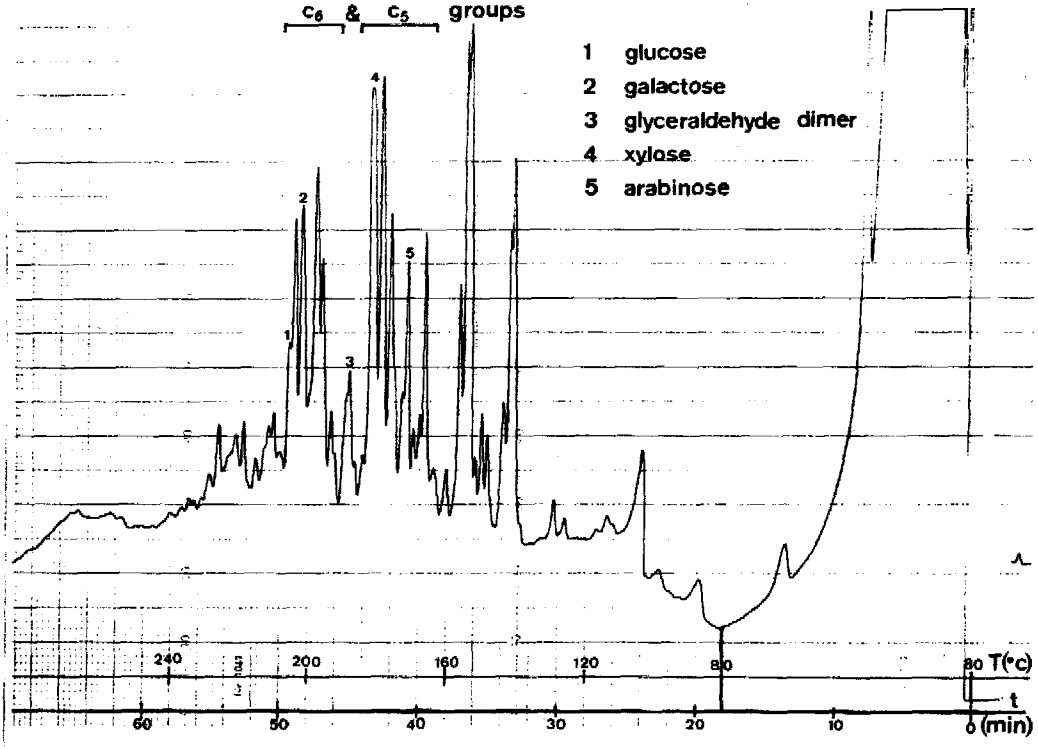
b) "Formoin mixtures" prepared according to the specified conditions, consist mostly of C_5 and C_6 carbohydrates and further additions of formaldehyde to the reacting mixtures does not produce a substantial increase on the proportion of longer chain components.

c) Use of reference samples establishes, beyond any reasonable doubt, the presence of glucose, galactose, glyceraldehyde dimer, xylose and arabinose in "formoin mixtures". A typical gas chromatogram is shown in the figure.

d) Extensive m.s. studies on about twenty of the main chromatographic peaks, show no similiarity with reported spectra of branched-chain sugars[6].

On the base of analogy reasoning, it can be concluded that the benzoin-like autocondensation of formaldehyde should afford formoin, that is to say, glycolaldehyde, according to the sequence given in the scheme. Glycolaldehyde can then enter into further benzoin-like condensations, similarly catalyzed by the conjugate base of the thiazolium ion which is present in the medium: reaction of glycolaldehyde with formaldehyde can afford glyceraldehyde and dihydroxyketone and reaction with itself, will afford ketotetrose. Further condensations are now possible, new hydroxyaldehydes (aldoses) being formed only in those reactions in which formaldehyde acts as the carbonyl affording moiety; all other condensations will lead to hydroxyketones (ketoses). On the other hand, possible rearrangements induced by the reversibility of the benzoin condensation (in biochemical parlance, induced by the transketolase activity of the catalyst[7]), should not be ignored.





Column: SE52, 3%, on Chromosorb W 60/80 mesh, 2m x 0.125"

Two reasonable assumptions can be made, which help on understanding the composition of "formoin mixtures":

a) The Lapworth intermediate (I) does not attack ketone carbonyl groups. This assumption is based on the fact that, up to now, no branched-chain products have been isolated in any benzoin condensation (neither with aromatic nor with aliphatic aldehydes). According to this assumption, ketoses should be stable end products, that is to say, no branched-chain sugars should be present in "formoin mixtures".

b) The Lapworth intermediate (I) does not react, or reacts slowly, with aldohexoses, due to the predominance of hemiacetal forms (masked aldehyde carbonyl groups). This assumption explains the low concentration of sugars with chains longer than C_6.

Exploratory studies using sodium cyanide in DMF, in the presence of a crown-ether, seem to afford not identical but comparable results with those here reported. Experiments using chiral thiazolium salts are in progress, as well as biological assays with "formoin mixtures".

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