Carbohydrate Research, 116 (1983) 197–207
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

THE FORMOIN REACTION

JOSEP CASTELLS, FRANCISCO LÓPEZ-CALAHORRA, AND FERNANDO GEIJO

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, Diagonal 647, Barcelona-28 (Spain)

(Received April 7th, 1982; accepted for publication, October 19th, 1982)

ABSTRACT

The formoin reaction, *i.e.*, the autocondensation of formaldehyde in an aprotic solvent catalysed by the conjugate base of a thiazolium ion, has been studied in detail. Glucose, galactose, dihydroxyacetone dimer, xylose, and arabinose have been identified as products. The influence of catalysts, temperature, basicity, and reaction time is documented. *N*,*N*-Dimethylformamide is a more convenient solvent than ether, benzene, or diglyme. Ethyldi-isopropylamine affords better yields of carbohydrate material than triethylamine. At $\leq 60°$, aldol condensations are reduced to a minimum. After 1–2 h of reaction (depending on the conditions), the yields begin to decrease and become zero after ~24 h.

INTRODUCTION

Since Butlerow's first report[1] in 1861 on the calcium hydroxide-catalysed condensation of formaldehyde to give a complex mixture of carbohydrates, this reaction has been of interest in relation to photosynthesis, the primordial origin of monosaccharides, the industrial manufacture of edible carbohydrates, and the continuous recycling of metabolic CO_2 and H_2O during sustained space-flight[2].

The term "formose reaction" includes the Butlerow reaction and its modifications, all of which take place in alkaline aqueous or alcoholic solutions, and the term "formose mixture" (or formose) connotes the mixtures of monosaccharides formed in those reactions; the term formose was first used by Loew[3].

Formose mixtures are complex (~30 components) because, during the formose reaction, several processes occur, such as aldol-type condensations of formaldehyde, hydroxyaldehydes, and hydroxyketones, Lobry de Bruyn–Alberda van Ekenstein rearrangements, mutarotations, and Cannizzaro reactions. These reactions lead to branched and unbranched carbohydrates up to at least C_8 in size. Because of the presence of large quantities of branched-chain carbohydrates, formose mixtures are highly toxic.

Since the formose reaction was reviewed[4], activity in this field has continued[5]. Most of the current efforts are directed to identifying conditions under which the formose reaction becomes more selective. When the formose reaction

0008-6215/83/$ 03.00

was carried out[5e] in the presence of small amounts of Ca^{2+} and D-fructose, three compounds were formed with high selectivity, namely, 2-(hydroxymethyl)glycerol, 3-(hydroxymethyl)pentane-1,2,3,4,5-pentol and 2,4-bis(hydroxymethyl)pentane-1,2,3,4,5-pentol. When diethylaminoethanol was used[5c] as catalyst, pentaerythritol was the exclusive product.

If the formose reaction is to be used for the synthesis of edible sugars, a new approach to the autocondensation of formaldehyde is required. The benzoin condensation, which involves the cyanide-catalysed condensation of the corresponding aldehydes, can be extended to aliphatic aldehydes[6] if the conjugate base of a thiazolium ion is used as catalyst. We now report on the catalytic action of the conjugate base of a thiazolium ion on formaldehyde (formoin reaction[7]) as a new route to carbohydrates.

RESULTS AND DISCUSSION

When a mixture of paraformaldehyde, triethylamine, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (thiazolium salt), and *N*,*N*-dimethylformamide was kept at 100°, a complex mixture of products was obtained which, after

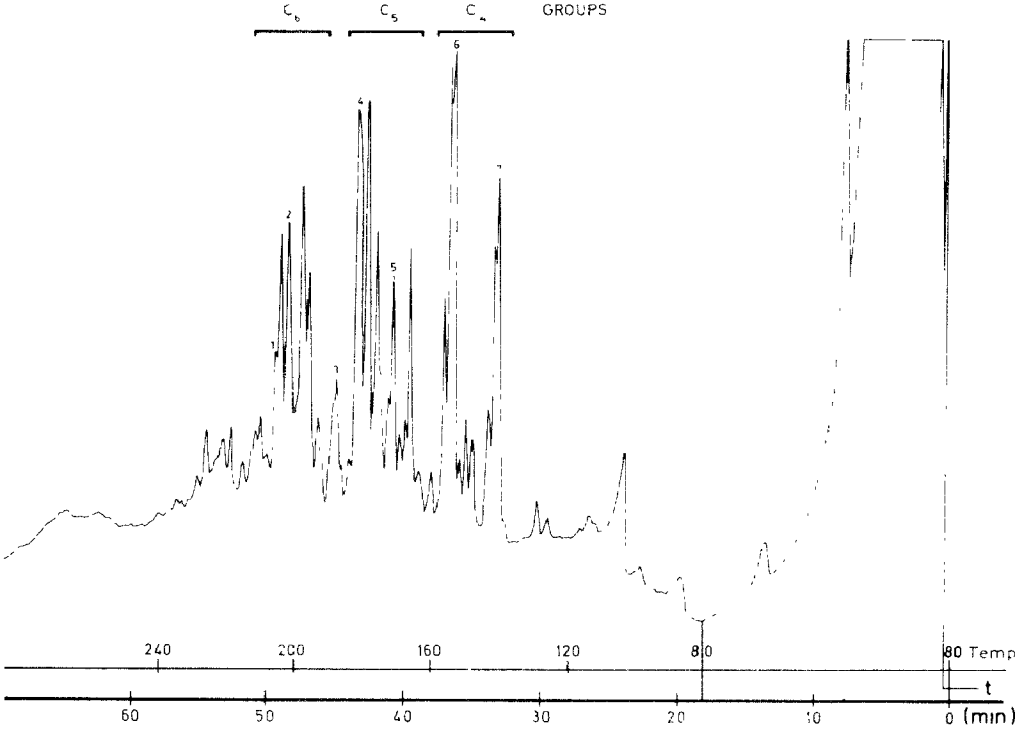
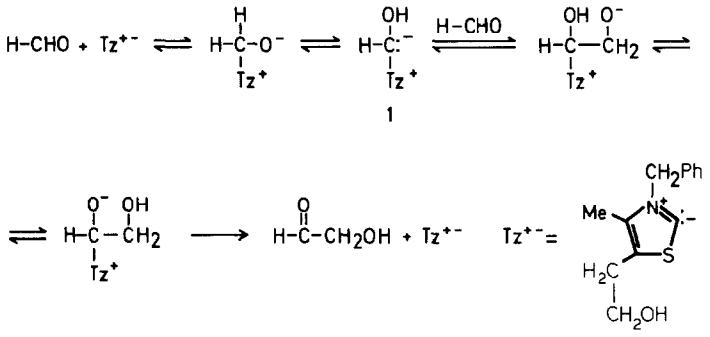


Fig. 1. Gas chromatogram of a trimethylsilylated formoin mixture prepared as described in the Experimental (general reaction): 1, glucose; 2, galactose; 3, dihydroxyacetone dimer; 4, xylose; 5, arabinose; 6, erythrulose; 7, erythrose–threose



Scheme 1 First stage of the formoin reaction

trimethylsilylation, was subjected to g.l.c. (Fig. 1) and g.l.c.–m.s. Investigation of about twenty of the main chromatographic peaks established (*a*) the carbohydrate nature of the products that they contained[8], (*b*) the absence of any mass-spectral characteristics of branched-chain sugars[9], (*c*) the identity of some carbohydrates, and (*d*) a clear-cut division of the chromatograms into C_n regions. It was concluded that the formoin mixture consisted mostly of C_5 and C_6 carbohydrates. The components in peaks 1 (glucose), 2 (galactose), 3 (dihydroxyacetone dimer, formerly[7] thought to be glyceraldehyde dimer), 4 (xylose), and 5 (arabinose) were identified by comparison with authentic compounds (lyxose was not available for comparison with the last two products). Peak 7 contained erythrose and/or threose, since these tetroses could not be distinguished on the basis of retention time and mass spectra. M.s. showed that the substance in peak 6 was a C_4 carbohydrate different from erythrose and threose; since the same substance was obtained by condensation of glycolaldehyde in the presence of thiazolium salt, it was concluded to be erythrulose.

The first product of the formoin reaction should be glycolaldehyde, as shown in Scheme 1. Glycolaldehyde can then react with formaldehyde to afford trioses, and with itself to give erythrulose. Subsequently, the reaction of glyceraldehyde with formaldehyde will afford aldotetroses, with glycolaldehyde will give pentos-2-uloses and pentos-3-uloses, and with itself will yield four hexos-3-uloses. The result of further condensations is not difficult to predict.

For C_6 and smaller molecules, and considering only acyclic structures, 29 products are possible in the formoin reaction. Moreover, the reversibility of the condensation reactions (*cf.* transketolase-mediated reactions[10]) represents a secondary source of carbonyl compounds that may facilitate the formation of carbohydrates not allowed by the kinetics of the main route.

The formation of multiple chromatographic peaks after trimethylsilylation of individual carbohydrates is well known[11]. Studies are in progress to apply to formoin mixtures the simplifying derivatisation-procedures proposed by Seymour[12].

Product mixtures from a given carbohydrate have a composition which de-

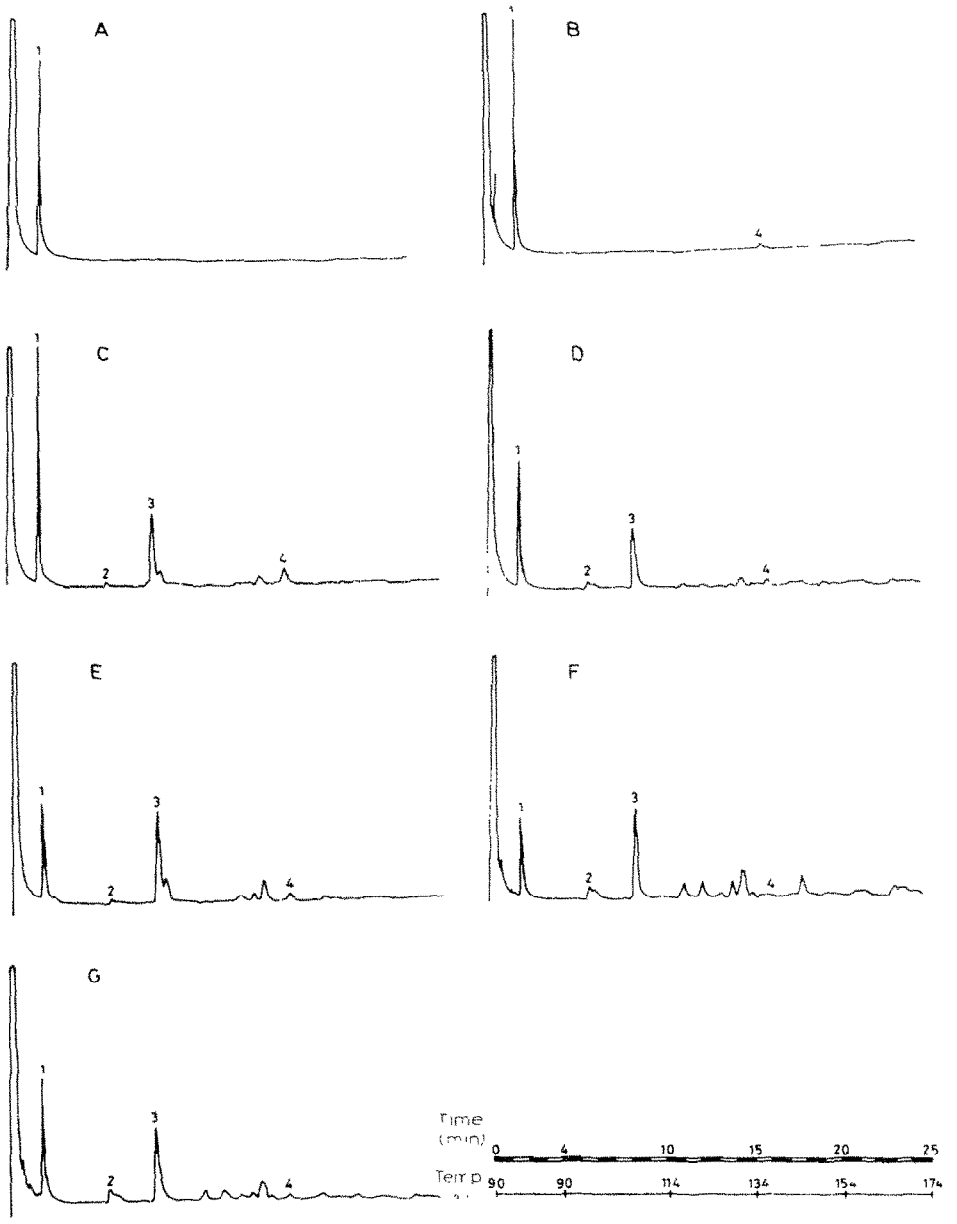


Fig. 2. Dependence of the complexity of formoin mixtures on the concentration of paraformaldehyde. Gas chromatograms of trimethylsilylated formoin mixtures from experiments in which the paraformaldehyde to catalyst ratio was 14.6:1 (A and B, 4 and 24 h at 60°, respectively), 157:1 (C and D, 4 and 24 h at 60°, respectively), and 235:1 (E and F, 4 and 24 h at 60°, respectively; G, 1.5 h at 110°). 1, glycolaldehyde; 2, erythrose–threose; 3, erythrulose; 4, dihydroxyacetone dimer.

pends on the solvent and reaction temperature. The isomeric composition of solutions of glucose or fructose in *N*,*N*-dimethylformamide at 100–110° in the presence or absence of triethylamine or triethylamine and thiazolium salt, as in a standard formoin reaction, changes with time (changes in peak intensities). Differences in peak intensities were also observed between our chromatograms and those reported in the literature in which, as a rule, samples in pyridine solutions were silylated[11].

Glycolaldehyde, glyceraldehyde, and the tetroses gave rise to mixtures that were more complex than those from pentoses and hexoses[13], mainly because of the variety of possible dimeric forms (*e.g.*, 22 for DL-glyceraldehyde). Moreover, equilibrium was attained very slowly (hours or even days).

An important, common feature of formoin mixtures was that, invariably, C_7 and higher sugars were present in much lower proportion than C_5 and C_6 sugars, presumably because the Lapworth–Breslow intermediate (**1** in Scheme 1) does not react, or reacts slowly, with aldohexoses, due to the extreme preponderance of cyclic-hemiacetal forms. No formoin reaction occurred with glucose or fructose.

No branched sugars were detected in the formoin mixtures, and ketoses preponderated over aldoses; for example, major components in simple mixtures were dihydroxyacetone and erythrulose in addition to glycolaldehyde. Both findings can be explained by a general lack of reactivity of ketone carbonyl groups towards Lapworth–Breslow intermediates. This assumption is reasonable since, with one exception, no branched-chain products have been isolated from benzoin-type condensations with aromatic or aliphatic substrates. α-Acetolactate was formed when thiamine was incubated with pyruvate[10]. Apparently, a carbonyl group α to a carboxylate group can be attacked by a Lapworth–Breslow intermediate.

Because of the commercial availability of 5-(2-hydroxyethyl)-4-methylthiazole and its easy quaternisation with benzyl chloride, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride was the thiazolium salt normally used as catalyst. However, other thiazolium salts or analogues [thiamine, bi(3-methylbenzothiazolin-2-ylidene), 4-methyl-3-(2-phenylethyl)thiazolium iodide, *etc.*] have also been used.

When the ratio of paraformaldehyde to catalyst was 14.6:1, glycolaldehyde was formed together with traces of dihydroxyacetone, whereas, if the ratio was 157:1 or 235:1, more-complex mixtures resulted (Fig. 2). Thus, below a certain concentration, glycolaldehyde does not enter into a benzoin-type self condensation.

The formoin reaction occurred only when an aprotic solvent was used. *N*,*N*-Dimethylformamide was the solvent of choice; ether was too volatile, diglyme was more difficult to remove than *N*,*N*-dimethylformamide, and benzene gave rise to a heterogeneous system. When such protic solvents as methanol and ethanol were used, no sugar formation was detected, possibly because the formaldehyde was converted into hemiacetal and acetal forms[14].

The catalysts in the formoin reaction are the conjugate bases of thiazolium

ions generated when an organic base is added to the reaction medium. The added base, acting as such or as a nucleophile, can cause various side-reactions which undoubtedly contribute to the complexity of the formoin mixtures. Thus, under alkaline conditions, carbohydrates undergo Lobry de Bruyn–Alberda van Ekenstein transformations[15] (epimerisation of aldoses and ketoses, and aldose–ketose rearrangement). However, when glucose and fructose were subjected to formoin reaction conditions, no transformations of this kind occurred. Aldol condensations of short-chain sugars proceed rapidly in weakly alkaline solution[16]. Moreover, these reactions are reversible, so that retroaldol reactions of long-chain sugars followed by further aldol recombinations of fragments can occur.

Thermal depolymerisation of paraformaldehyde affords the monomer which serves as the substrate for the formoin reaction. However, formaldehyde can repolymerise under the action of a base such as triethylamine[17]:

$$Et_3N + CH_2O \rightarrow Et_3\overset{+}{N}\text{-}CHO \xrightarrow{CH_2O} Et_3\overset{+}{N}(CH_2O)_nCH_2O$$

The formation of ammonium–alkoxide betaines could account for certain low yields (~20%) in the formoin reactions (see Experimental) because of losses on deionisation. Gas chromatograms (*e.g.*, Fig. 1) of the trimethylsilylated products in aliquots withdrawn directly from the reaction mixture show an envelope from which individual peaks emerge. Ion pairs such as $Cl^- Et_3N^+(CH_2O)_nCH_2OSiMe_3$ could account for the envelope, which is much diminished when deionisation precedes derivatisation.

During the formoin reaction, thiazolium rings are cleaved with concomitant loss of catalytic activity; the initial step is nucleophilic attack at position 2 of the thiazolium ring and the stronger the nucleophile present in the reaction medium, the shorter the life of the thiazolium ring[18]. As a result of this ring cleavage, the ratio between thiazolium ion and base (initially 1:5) does not remain constant during the formoin reaction and only base remains after several hours of reaction.

The avoidance of aldol condensations in the formoin reaction is important, since this process can lead to toxic branched-chain sugars. At 100° with glycolaldehyde in *N*,*N*-dimethylformamide containing triethylamine, aldol condensation took place, yielding aldotetetroses. However, at 60° or below, there was no significant reaction during 2 h; at 60° when thiazolium salt was also present, erythrulose was formed.

With erythrose as starting material together with base or base and thiazolium salt, at 60° or below, no reaction occurred, whereas, at 80° or 100°, octuloses were formed (no significant formation of octuloses was observed in the formoin reactions).

Thus, aldol condensations can be minimised by working at 60° or below, and formoin reactions were conducted routinely at 60°. Fig. 2 shows that, with other parameters being kept constant, the lower the temperature the simpler the formoin mixture. Formoin reactions can be conducted even at room temperature.

TABLE I

YIELDS OF CARBOHYDRATES IN THE FORMOIN REACTION[a]

Expt.	*Temp. (degrees)*	*Mannitol (mg)*	*Base*	*Base (mg)*	*Paraform-aldehyde (mg)*	*Yield*[b]								
						Time (min)								*Time (h)*
						7	*14*	*22*	*50*	*70*	*140*	*240*	*420*	*24*
1	60	148.0	Et_3N	370	409.4		69					33		21
2	60	112.1	Et^iPr_2N	464	398.8									45
3	60	386 0	Et^iPr_2N	495	4083						100		67	41
4	64	156.6	Et^iPr_2N	464	403.4			66	82			52		53
5	85	142.8	Et^iPr_2N	465	393.8	100				100		55		0
6	85	131.3	Et^iPr_2N	506	459.5	100				100				0
7	85	599.0	Et_3N	400	4144		100		58			41		10

[a]Thiazolium salt (242–267 mg) and *N,N*-dimethylformamide (5 mL; 10 mL in 3) were used in each experiment [b]Expressed as mg of carbohydrate (including glycolaldehyde)/100 mg of paraformaldehyde.

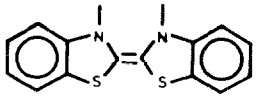
When the base was varied in formoin reactions conducted at 80°, the yields of deionised product were 15 (triethylamine), 35 (ethyldi-isopropylamine), 23 (1,4-diazatricyclo[2.2.2]octane), and 31% (1,5-diazabicyclo[3.4.0]non-5-ene). Thus, the lower the nucleophilicity of the base, the higher the yield of deionised product. Ethyldi-isopropylamine is associated with a yield in carbohydrate material substantially higher than that with triethylamine, although the basicities are similar.

In a subsequent series of experiments carried out at 60° without repetitive additions of formaldehyde, the resulting formoin mixtures were subjected to quantitative g.l.c. Under these conditions, the formoin reaction did not go further than the formation of dihydroxyacetone and erythrulose, and, beyond a certain reaction time, the yields decreased. The results are summarised in Table I.

The fall in yield on prolonged reaction may be explained as follows. Initially, the formoin reaction is faster than any other competing process, but, since the reaction is reversible, base-catalysed repolymerisation of formaldehyde will become increasingly important as the thiazolium ions are decomposed. Ethyldi-isopropylamine, which is less nucleophilic than triethylamine towards thiazolium ions, is less effective in inducing repolymerisation of formaldehyde.

The formoin reaction is a promising method for the conversion of formaldehyde into carbohydrates. Stereoselective benzoin condensations have been achieved by using chiral thiazolium salts[19] and the effect of such salts on the formoin reaction is being explored.

The presence of a base in the formoin reaction-medium is a disadvantage because of the base-catalysed side-reactions. However, the use of base can be circumvented, and Wanzlick *et al.*[20] and Metzger *et al.*[21] have described the preparation of such species as **2**, which are dimers of conjugate bases of thiazolium ions and show the same catalytic activity as the conjugate bases prepared *in situ* from thiazolium ions and base. Dimers of this type are excellent catalysts for the formoin reaction[22], and base-catalysed side-reactions are thus avoided.



2

EXPERIMENTAL

General methods. — Paraformaldehyde (Merck) was used throughout, since material from different sources did not exhibit uniform behaviour. 3-Benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride ("thiazolium salt") was used as catalyst and prepared[23] from 5-(2-hydroxyethyl)-4-methylthiazole (Merck) and benzyl chloride. Amines were purified by refluxing with benzenesulphonyl chloride and subsequent distillation; the absence of primary and secondary amines from the dis-

tilled product was confirmed by the $LiAlH_4$ test. *N,N*-Dimethylformamide was dried by refluxing over CaH_2, and the distilled product was stored over 4 Å molecular sieves. Analytical-quality pyridine was used, and stored over 4 Å molecular sieves.

Temperatures refer to external heating-baths.

Samples for g.l.c. were prepared[11] by mixing aliquots (0.5 mL) of reaction mixtures with pyridine (0.5 mL), hexamethyldisilazane (0.4 mL), and chlorotrimethylsilane (0.2 mL). The injected volume was 1 μL. A Carlo Erba Fractovap GT and a Hewlett-Packard 5710A chromatograph connected to a Hewlett-Packard 3390A integrator were used for g.l.c., and a Perkin–Elmer 990 chromatograph connected to a Hitachi RMU-6L mass spectrometer for g.l.c.–m.s. A column (2 m × 0.125 in.) packed with 3% of SE52 on Chromosorb W (60–80 mesh) was used with a temperature programme of 90° for 4 min, and then 4°/min.

Formoin reactions. — (a) General reaction. Paraformaldehyde (40 g; 1.33 mol of formaldehyde) was added with continuous stirring to a solution of triethylamine (18.8 g, 186 mmol) and thiazolium salt (12.5 g, 46 mmol) in *N,N*-dimethylformamide (250 mL) at 100° (dissolution of paraformaldehyde was almost instantaneous; in the absence of catalyst, no dissolution occurred). After 30 min at this temperature, more paraformaldehyde (10 g; 330 mmol) was added and this procedure was repeated twice more. The mixture was then neutralised with conc. HCl, the solvent was distilled *in vacuo*, and the resulting oil was poured into water and continuously extracted with ether for 12 h. The aqueous solution was treated thrice with active charcoal, deionised by using columns (30 × 3 cm) of Kastel A300 (HO^-) and C300 (H^+) resins, and concentrated. The resulting, viscous, yellow or reddish oil (15 g) was trimethylsilylated and subjected to g.l.c. (Fig. 1).

(b) Behaviour of glucose and fructose. A mixture of glucose or fructose (0.2 g, 1.1 mmol) and *N,N*-dimethylformamide (2.5 mL) was kept at 100–110°. Aliquots were withdrawn after 0.5, 1, and 5 h, trimethylsilylated, and subjected to g.l.c. and g.l.c.–m.s. The above reactions were repeated with the addition of triethylamine (0.188 g, 1.85 mmol), and triethylamine (0.188 g, 1.85 mmol) plus thiazolium salt (0.125 g, 0.46 mmol).

(c) Ethyldi-isopropylamine as base. A mixture of paraformaldehyde(0.52 g; 17.3 mmol of formaldehyde), base (0.57 g, 4.4 mmol), thiazolium salt (0.32 g, 1.2 mmol), and *N,N*-dimethylformamide (15 mL) was stirred vigorously at 60°. Aliquots for trimethylsilylation and g.l.c. were withdrawn after 4 and 24 h.

In subsequent reactions, the amount of paraformaldehyde was increased to 173 mmol (5.22 g) and 284 mmol (8.54 g). The last reaction was also carried out at 110° for 1.5 h.

The corresponding gas chromatograms are shown in Fig. 2.

(d) Kinetic experiments. A mixture of glycolaldehyde (0.04 g, 0.67 mmol) and 0.36M triethylamine in *N,N*-dimethylformamide (0.5 mol) was heated in a vessel provided with a septum, cooled, trimethylsilylated, and subjected to g.l.c. After 2

h at 60°, no reaction had occurred, but, after 1 h at 100°, erythrose and threose had been formed.

A similar mixture plus thiazolium salt (12 mg, 0.04 mmol) was heated and then analysed. After 1 h at 60°, erythrulose had been formed; after 1 h at 100°, erythrose and threose were present.

In parallel experiments where erythrose (0.08 g, 0.67 mmol) was used instead of glycolaldehyde, no reaction occurred at 60°, but octuloses were formed at 100°.

(e) Variation of nitrogen base. A mixture of paraformaldehyde (1.5 g; 50 mmol of formaldehyde), base (3.4 mmol), thiazolium salt (0.25 g, 0.93 mmol), and *N*,*N*-dimethylformamide (5 mL) was kept at 80°, and more (1.5 g; 50 mmol) paraformaldehyde was added after 0.5, 1, 1.5, and 2 h. After heating for a further 0.5 h, the reaction mixture was worked-up as in *(a)*. The bases used and yields attained are given in the Discussion.

(f) Quantitative analyses. These experiments were conducted at 60° with a single addition of paraformaldehyde and with the addition of a known weight of mannitol as internal standard. Response factors (for trimethylsilyl derivatives) relative to that of mannitol were determined by using mixtures of mannitol and carbohydrates of known composition.

The results are included in Table I.

ACKNOWLEDGMENTS

We thank Miss Anna Casanovas for help in performing g.l.c.–m.s. and interpreting the results, Hispano Química, S.A., for access to its mass spectrometer, Instituto Nacional de Asistencia y Promoción del Estudiante (Spain) for a scholarship (to F.G.), and the Universitat de Barcelona and the Comisión Asesora de Investigación Científica y Técnica for financial assistance

REFERENCES

1 A. BUTLEROW, *C. R. Acad. Sci.*, 53 (1861) 145–147
2 A. H. WEISS AND J. SHAPIRA, *Hydrocarbon Process.*, 49 (1970) 119–126
3 O. LOEW, *Ber.*, 22 (1889) 470–478, 39 (1906) 1592–1593
4 T. MIZUNO AND A. H. WEISS, *Adv. Carbohydr. Chem. Biochem.*, 29 (1974) 173–227
5 *(a)* G. HARSCH, W. VOELTER AND H. BAUER, *Z. Naturforsch., Teil B*, 32 (1977) 826–832; *(b)* T. I. KHOMENKO, O. A. GOLOVINA, M. M. SAKHAROV, O. V. KRYLOV, AND A. H. WEISS, *React. Kinet. Catal. Lett.*, 13 (1980) 407–412, *(c)* T. MATSUMOTO, M. KOMIYAMA, AND S. INOUE, *Chem. Lett.*, (1980) 839–842; *(d)* A. G. OSINOVSKY AND B. V. EROFEEV, *Dokl. Akad. Nauk BSSR*, 25 (1981) 620–623, *(e)* Y. SHIGEMASA, T. TAII, F. WAKI, AND R. NAKASHIMA, *Bull. Chem. Soc. Jpn.*, 54 (1981) 1403–1409
6 H. STETTER, R. Y. RAMSCH AND H. KUHLMANN, *Synthesis*, (1976) 733–735
7 J. CASTELLS, F. GEIJO AND F. LOPEZ-CALAHORRA, *Tetrahedron Lett.*, (1980) 4517–4520
8 A. E. PIERCE, *Silylation of Organic Compounds*, Pierce Chemical Company, Rockford, IL, 1968
9 R. D. PARTRIDGE, A. H. WEISS AND D. TODD, *Carbohydr. Res.*, 24 (1972) 29–44
10 T. C. BRUICE AND S. BENKOVIC, *Bioorganic Mechanisms*, Vol. II, Benjamin New York, 1966, p. 181

11 C. C. SWEELEY, R. BENTLEY, M. MAKITA, AND W. W. WELLS, *J. Am. Chem. Soc.*, 85 (1963) 2497–2507.
12 F. R. SEYMOUR, E. C M. CHEN, AND S. H. BISHOP, *Carbohydr. Res.*, 73 (1979) 19–45; F. R. SEYMOUR, E. C. M CHEN, AND J E. STOUFFER, *ibid.*, 83 (1980) 201–242.
13 S. J. ANGYAL AND R. G WHEEN, *Aust. J. Chem.*, 33 (1980) 1001–1011, and references therein; D. GARDINER, *Carbohydr. Res.*, 2 (1966) 234–239.
14 W DANKELMAN AND J. M. H. DAEMEN, *Anal. Chem.*, 48 (1976) 401–404.
15 E. F. L. J ANET, in W. PIGMAN AND D. HORTON (Eds.), *The Carbohydrates: Chemistry and Biochemistry*, Vol. IA, Academic Press, New York, 1972, p. 175.
16 E. F. L J. ANET, in W. PIGMAN AND D. HORTON (Eds), *The Carbohydrates: Chemistry and Biochemistry*, Vol. IA, Academic Press, New York, 1972, p. 189; E. WESTERLUND, *Carbohydr. Res.*, 91 (1981) 21–30.
17 M. A. MARKEVICH, P. I PENCHEV, N. F. KEDRINA, V. V. IVANOV, AND N. J. ENIKOLOPYAN, *Dokl. Akad. Nauk SSSR*, 190 (1970) 1140–1142.
18 G D MAIER AND D. E. METZLER, *J. Am. Chem. Soc.*, 79 (1957) 4386–4391; E. YATCO-MANZO, F. RODDY, R. G. YOUNT, AND D. E. METZLER, *J. Biol Chem.*, 234 (1959) 733–737; R. G. YOUNT AND D. E METZLER, *ibid.*, 234 (1959) 738–741.
19 J. C. SHEEHAN AND T. HARA, *J. Org. Chem.*, 39 (1974)1196–1199.
20 H.-W. WANZLICK AND H.-J. KLEINER, *Angew. Chem* , 75 (1963) 1204; H.-W. WANZLICK, H.-J. KLEINER, I. LASCH, H. U. FULDNER, AND H. STEINMAUS, *Justus Liebigs Ann. Chem.*, 708 (1967) 155–165; B. LACHMAN, H. STEINMAUS, AND H -W. WANZLICK, *Tetrahedron*, 27 (1971) 4085–4090.
21 J METZGER, H. LARIVÉ, R. DENNILAULER, R. BARELI E, AND C. GAURAT, *Bull. Soc. Chim Fr.*, (1964) 2857–2867.
22 J CASTELLS, F. LÓPEZ-CALAHORRA, AND F. GEIJO, unpublished results.
23 H. STETTER AND H. KUHLMANN, *Synthesis*, (1975) 379–380.