The Enhancement of Formose Formation with 2-Hydroxyacetophenone. A Mechanism Involving Aldol and Retro-aldol Reactions

Tomoya SAKAI,* Masahiko ISHIZAKI, and Masafumi GOTO

Department of Chemical Reaction Engineering, Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467

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The rapid aldol addition of formaldehyde to 2-hydroxyacetophenone (HAP), an efficient accelerator for formose formation, took place to yield addition products of HAP with one and two molecules of formaldehyde at 35 °C in an aqueous 40% methanol mixture of formaldehyde, HAP, and $Ca(OH)_2$. No further addition product with more than two molecules of formaldehyde attached to HAP was detected throughout the reaction. On the contrary, benzaldehyde and benzoic acid were formed, accompanied by formose sugars. The initial molar amount of HAP corresponded to the sum of the compounds substituted with the phenyl group including benzaldehyde and benzoic acid. The retro-aldol reaction of the HAP derivatives is likely to be involved in the overall reaction to yield glycolaldehyde or trioses, which are good accelerators for formose formation.

Formose formation in an aqueous mixture of formaldehyde(C_{1A}) and $Ca(OH)_2$ at 50—60 °C reveals an autocatalytic feature: an S-shaped profile of the C_{1A} conversion *vs.* the reaction time. This characteristic feature arises from the slow dimerization of C_{1A} to form glycolaldehyde(C_{2A}) and a successive rapid aldol addition of C_{1A} to C_{2A}.

It is well known[1] that the introduction of compounds which have the structure of R–CO–CH_2OH or R–CH(OH)–CHO to the above reaction mixture enhances the formose formation by shortening the induction period and accelerating the successive consumption of C_{1A}. The initial step has been reported to be the addition of C_{1A} to the accelerator.[2] The order of efficiencies of accelerators has been evaluated by Langenbeck as follows : 2-hydroxyacetophenone (HAP)>2-hydroxy-2′-acetonaphthone> 1-hydroxy-2-propanone> 1,3-dihydroxyacetone (C_{3K}) > C_{2A} > 5-hydroxyacetylacenaphthene>D-fructose>D-glucose.[3] HAP is a unique accelerator because of its high efficiency and its structure containing a phenyl group. HAP seems to be a good candidate for analyzing the action of the accelerators because it is easy, with the accelerator, to distinguish the addition products of C_{1A} from the usual formose sugars by tracing the phenyl group among the products.

In this paper we describe the identification of addition products of C_{1A} with HAP and the change in the amounts of the products originated from HAP with the reaction time. No product with more than two molecules of C_{1A} attached to HAP was detected. On the contrary, degraded products, such as benzaldehyde and benzoic acid, were formed, accompanied by low-molecular-weight formose sugars. These observations suggest that the C–C bond dissociation of HAP derivatives through retro-aldol reaction is essential for the acceleration.

Experimental

Materials. The reagents, formaldehyde (C_{1A}), 1,3-dihydroxyacetone (C_{3K}), HAP, and $Ca(OH)_2$, were the same as those described previously.[4] Guaranteed-grade NaOH, $CaCl_2$, $NaBH_4$, $Si(CH_3)_3Cl$, D-fructose, and hexamethyldisilazane were used as received from Wako. The pyridine (Wako) was dried with molecular sieve 4A.

The 2,3-dihydroxypropiophenone (DHPP) was prepared according to the method of Cahnmann;[5] mp 78 °C (lit, 81.5 °C; softening point 78 °C).[5]

Formose-formation Procedure. The reaction was conducted following the "normal procedure" described previously.[4] An aliquot of the reaction mixture was periodically withdrawn from the flask and was neutralized with a dilute hydrochloric acid to quench the reaction.

Product Analyses. The C_{1A} and formic acid were determined by the use of a high-performance liquid (HPL) chromatograph, as has been described previously.[4] The benzoic acid and benzaldehyde were analyzed with an Ohkura 701 gas liquid chromatograph (GLC) equipped with a FID detector and a Silicone Grease (SE-30) column at 130 °C. Biphenyl was used as the internal standard. The other products were determined as trimethylsilyl derivatives after the reduction of the reaction mixture with $NaBH_4$[6] using the same GLC by increasing the temperature from 100 to 250 °C at the rate of 2 °C min^{-1}. Phenethyl alcohol was added as an internal standard prior to the trimethylsilylation. Several peaks detected in the GL chromatogram were identified by means of GLC-mass spectrometry employing a Hitachi M-52 mass spectrometer. The area of the GL chromatogram of each equimolar amount of C_{3K}, DL-glyceraldehyde (C_{3A}), glucose, HAP, and DHPP after the trimethylsilylation was confirmed to be proportional to the molecular weight; accordingly, the amounts of the product appearing in the GL chromatogram were determined on the basis of this proportionality. The amount of C_{2A} might be estimated too low, however, because of a partial loss during the evaporation of the reaction mixture.

The conversion of C_{1A} to formose (%) is defined by means of Eq. 1;

$$C_{1A}\text{ conversion to formose }(\%) = \left(1 - \frac{[C_{1A}]_{remained} - [HCOOH]}{[C_{1A}]_{initial}}\right) \times 100. \quad (1)$$

The recovery of C_{1A} (%) is defined by Eq. 2:

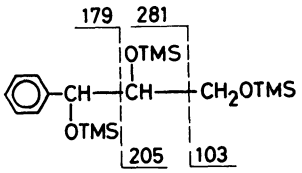
$$\text{Recovery of } C_{1A}(\%) = \{([C_{1A}]_{remained} + [HAPC_1] + 2[HAPC_2] + \sum_{n=2}^{7} n[C_n] - 6[Fru]_{initial} + [HCOOH])/[C_1]_{initial}\} \times 100, \quad (2)$$

where $HAPC_1$ and $HAPC_2$ represent the addition products of one and two molecules of C_{1A} respectively with HAP, where C_n represents the carbohydrates of n carbon atoms, and where Fru represents D-fructose.

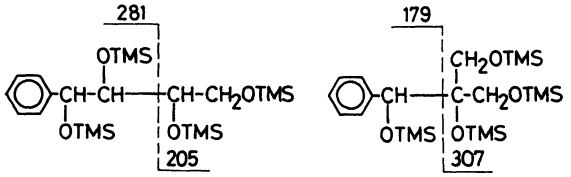
Results and Discussion

A typical GL chromatogram of the reaction mixture after reduction and trimethylsilylation is shown in Fig. 1. The four peaks indicated by arrows appeared exclusively in the presence of HAP. The other peaks are those found in the usual $Ca(OH)_2$-catalyzed formose formation. The peaks are resolved for trimethylsilylated sugar alcohols according to the differences in carbon numbers and in either a straight (s) or branched (b) carbon skeleton of sugar alcohols. Therefore, the peaks are denoted as C_{4s} and so on, where C_{4s} represents tetroses with a straight carbon chain.

The four peaks originating from HAP were identified by means of GLC-mass spectrometry. Characteristic mass fragments measured for the peaks indicated as $HAPC_1$, $HAPC_2$(s), and $HAPC_2$(b) in the GLC are tabulated in Table 1. The presence of strong fragments of $m/e=103$, 205, and 307 has been reported to indicate $-CH_2OTMS$, $-CH(OTMS)-CH_2OTMS$, and $-C(OTMS)(-CH_2OTMS)_2$ respectively, where OTMS stands for $OSi(CH_3)_3$.[7] The peak denoted as $HAPC_1$ was identical to the sample derived from DHPP. The characteristic main fragments of $m/e=281$, 205, 179, and 103 are in accordance with the bond scissions shown below, as well as the fragment of $m/e=295$ (M−OTMS).



The peaks denoted as $HAPC_2$(s) and $HAPC_2$(b) showed a mass fragment of $m/e=383$(M−CH_2OTMS). The former has mass fragments of 281 and 205, similar to those of the $HAPC_1$ peak. On the contrary, the latter is characterized by the main fragments of 307 and 179, together with a strong fragment of 218(307−OTMS). These fragmentations are in accordance with the respective bond scissions of the straight and branched structures, as is shown below:



$HAPC_2$(s) Peak $HAPC_2$(b) Peak

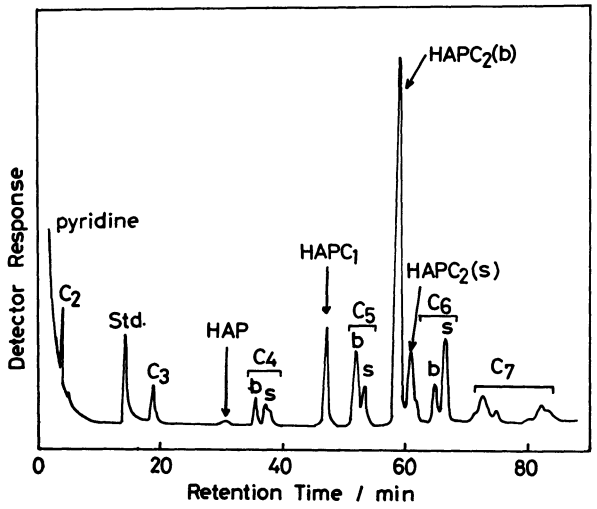


Fig. 1. A typical GL chromatogram of the products at the reaction time of 10 min after reduction with $NaBH_4$ and trimethylsilylation. 35 °C, 40 vol % CH_3OH–H_2O, $Ca(OH)_2$; 0.10 mmol cm^{-3}, C_{1A}; 1.0 mmol cm^{-3}, HAP; 0.20 mmol cm^{-3}.

Table 1. Mass fragments of reduced and trimethylsilylated DHPP, $HAPC_1$, $HAPC_2$(s), and $HAPC_2$(b)

Mass fragment in m/e					
$HAPC_1$, DHPP		$HAPC_2$(s)		$HAPC_2$(b)	
—		383	(w)	383	(w)
—		382	(w)	382	(w)
—		308	(w)	308	(w)
—		—		307	(st)
295	(st)	295	(w)	—	
281	(m)	281	(st)	—	
—		—		280	(m)
—		—		218	(st)
205	(st)	205	(m)	—	
—		—		204	(m)
179	(st)	179	(m)	179	(st)
149	(m)	149	(m)	149	(m)
116	(m)	116	(m)	—	
—		—		115	(m)
103	(m)	103	(w)	103	(st)
90	(w)	90	(m)	—	
73	(m)	73	(m)	73	(m)

st: Strong, m: medium, w: weak.

These characteristic fragmentations lead to the identifications of the $HAPC_2$(b) peak and $HAPC_2$(s) peak with tetrakis-*O*-trimethylsilyl-1-phenylerythritol and tetrakis-*O*-trimethylsilyl-1-phenyl-2-(hydroxymethyl)glycerol respectively. These results show that the addition products of C_{1A} with HAP belong to three classes of compounds which give 1-phenylglycerol, 2-(1-hydroxybenzyl)glycerol, and 1-phenyl-erythritol by reduction with $NaBH_4$. $HAPC_1$, $HAPC_2$(s), and $HAPC_2$(b) are, therefore, mixtures of phenyl-substituted sugars with the straight or branched carbon skeleton mentioned above.

The absence of compounds having a branched carbon skeleton for $HAPC_1$ in the product is worth notice.

The change in the amounts of HAP and its derivatives during the reaction is shown in Fig. 2. The rapid formation of $HAPC_1$ is the initial step of the reaction, followed by the formation of $HAPC_2$(b), presumably through a successive addition of C_{1A} to $HAPC_1$. Both $HAPC_1$ and $HAPC_2$(b) reach their maxima within

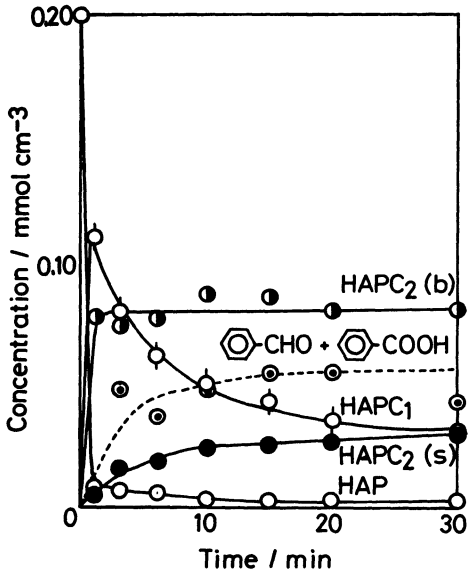


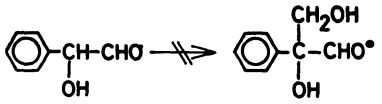
Fig. 2. Consumption of HAP and formations of $HAPC_1$, $HAPC_2$ (b), and $HAPC_2$ (s), and benzaldehyde+ benzoic acid. 35 °C, 40 vol % CH_3OH–H_2O, $Ca(OH)_2$; 0.10 mmol cm^{-3}, C_{1A}; 2.45 mmol cm^{-3}, HAP; 0.20 mmol cm^{-3}.

1 min after the addition of HAP to the mixture of $Ca(OH)_2$ and C_{1A}. The amount of $HAPC_1$ gradually decreases thereafter, but that of $HAPC_2$(b) is kept at *ca.* 0.8 mmol cm^{-3}. The formation of $HAPC_2$(s) appears to be slow, but its amount continues to increase as the reaction proceeds. As $HAPC_1$ decreases and $HAPC_2$(s) increases, benzaldehyde, benzoic acid, and low-molecular-weight formose sugars are formed in the reaction mixture. The summation over the molar amounts of HAP, $HAPC_1$, $HAPC_2$(s), $HAPC_2$(b), benzaldehyde, and benzoic acid was in agreement with the molar amount of HAP initially introduced.

The above observations suggest successive C_{1A} additions to HAP to form phenyl-substituted carbohydrates. However, no HAP derivative with more than two molecules of C_{1A} added to HAP was detected throughout the reaction. The occurrence of benzaldehyde and benzoic acid, accompanied by the simultaneous production of low-molecular-weight formose sugars, suggests the important role of the retro-aldol reaction of the phenyl-substituted carbohydrates. Benzaldehyde is expected to change to benzoic acid under the present reaction conditions, as will be discussed later.

A reaction scheme is drawn in Fig. 3 based on the aldol addition, retro-aldol reaction, and Lobry de Bruyn-Alberda van Ekenstein (LA) transformation, to which HAP and its derivatives are susceptible under basic conditions. In this scheme, $HAPC_1$ corresponds to either DHPP, **2**, and/or **3** : $HAPC_2$(s) corresponds to either **5**, **6**, **7**, and/or **8**, and $HAPC_2$(b) corresponds to either **4** and/or **9**.

HAP can undergo LA transformation, yielding 2-phenylglycolaldehyde (**1**) as has been reported previously,[4] and can undergo aldol addition, yielding DHPP. The results of GLC-mass spectrometry exclude the aldol addition of C_{1A} to **1** to form products possessing a

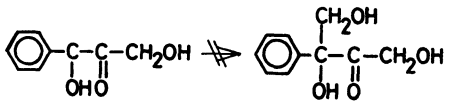


(3)

1

branched carbon skeleton, as is shown above. $HAPC_1$ and DHPP coincided exactly in the results of GLC and mass fragmentation data on reduction and trimethylsilylation. DHPP will isomerize to two isomers, 1-phenyl-1,3-dihydroxyacetone (**2**) and 3-phenylglyceraldehyde (**3**), through LA transformation and will undergo aldol addition with C_{1A} to yield 2-benzoylglycerol (**4**). The last compound can not add further C_{1A} because no hydrogen is available at the α-carbon atom to the carbonyl group. The retro-aldol reaction of DHPP can not be disregarded because a small amount of HAP remained throughout the reaction, as is shown in Fig. 2.

One of the tautomers of DHPP, **2**, which does not undergo retro-aldol reaction, adds C_{1A}, leading to 1-phenyl-2-ketotetrose (**6**). The product, **6**, can isomerize to three isomers; 1-benzoylglycerol (**5**), 4-phenyl-2-ketotetrose (**7**), and 4-phenylaldotetrose (**8**) and can undergo the retro-aldol reaction to yield C_{1A} and **2**. Compounds **5**, **7**, and **8** can degrade to C_{2A} and HAP, C_{3K} and benzaldehyde, C_{2A} and **1**, respectively, through retro-aldol reactions. The aldol addition of C_{1A} at the carbon atom adjacent to a phenyl group can be excluded in line with the fact that Eq. 3 scarcely proceeds.



(4)

2

The last tautomer of DHPP, **3**, decomposes to yield C_{2A} and benzaldehyde through retro-aldol reaction and undergoes aldol addition with C_{1A}, yielding a product, **9**, which can not be distinguished from **4** on reduction and trimethylsilylation. Compounds **9** decomposes to C_{3A} and benzaldehyde through the retro-aldol reaction.

The rapid formation of $HAPC_1$ and $HAPC_2$(b) suggests that the entities of $HAPC_1$ and $HAPC_2$(b) in the early stage of the reaction (less than 1 min) are DHPP and 2-benzoylglycerol (**4**) respectively. The aldol addition of C_{1A} to the carbon atom next to the carbonyl group seems to proceed quickly. The compound, **4**, is a terminal product in respect to the aldol addition, and its amount can be equilibrated by means of a retro-aldol reaction. The slow decrease in [$HAPC_1$] is accounted for by the loss of the tautomers of DHPP, **2** and **3**, due to the aldol additions and the retro-aldol reaction.

It is uncertain at present which is the main path for the production of benzaldehyde among retro-aldol reactions of **3**, **7**, and **9**. Benzaldehyde will be oxidized to benzoic acid under the present reaction conditions. The ratio of [benzaldehyde] to [benzoic acid] decreased from 1 : 9 in the early stage to 0.5 : 9.5 in the later stage. The absence of benzyl alcohol indicates that

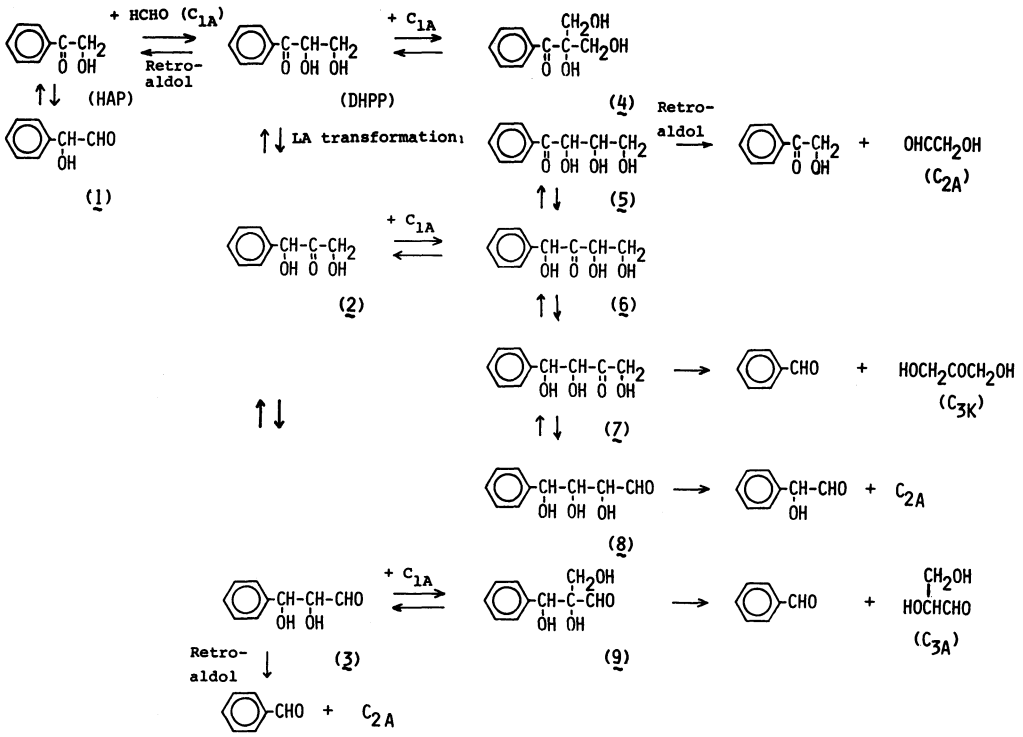


Fig. 3. A reaction scheme based on aldol addition, retro-aldol reaction and LA transformation.

benzoic acid is produced from benzaldehyde through cross-Cannizzaro reaction with aldoses and ketoses, as well as with C_{1A}.

The C_{1A} conversion to formose is plotted in Fig. 4 against the time in order to compare the reaction accelerated by HAP with that by C_{3K}, both in equimolar amounts. The initial rate in the presence of HAP exceeds that of C_{3K}, but the rate after *ca.* 1.5 min for the former is comparable to the initial rate for the latter. The amounts of C_{1A} consumed are 0.64 and 1.23 mmol cm^{-3} at 1 and 3 min respectively for an HAP-accelerated reaction, while the amounts of C_{1A} added to HAP are estimated to be 0.28 and 0.26 mmol cm^{-3} at 1 and 3 min respectively (Fig. 2). The remaining amounts of C_{1A}, 0.36 and 0.97 mmol cm^{-3} at 1 and 3 min respectively should have been converted to formose sugars which do not contain the phenyl group.

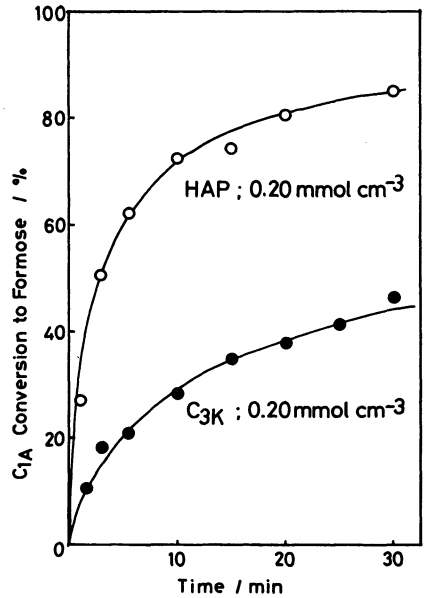


Fig. 4. Profiles of C_{1A} conversion to formose with HAP and C_{3K} as accelerators. 35 °C, 40 vol% CH_3OH–H_2O, $Ca(OH)_2$; 0.10 mmol cm^{-3}, C_{1A}; 2.45 mmol cm^{-3}, HAP or C_{3K}; 0.20 mmol cm^{-3}.

The sum of the amounts of benzaldehyde and benzoic acid in Fig. 4 is smaller than the amounts of glyceraldehyde and trioses estimated from the amount of C_{1A} converted to formose at 1 and 3 min. On the other hand, the dimerization of these low-molecular-weight sugars is expected to proceed more slowly than the C_{1A} addition to these sugars due to a high concentration of C_{1A} in the reaction mixture. Therefore, the efficient catalytic cycle of HAP *via* an intermediate, **5** or **8** (Fig. 3), can not be discarded at present.

The large initial consumption rate of C_{1A} in the presence of HAP is caused by the rapid aldol addition of C_{1A} to HAP; *i.e.*, HAP acts as a substrate. However the C_{1A} addition products of HAP are susceptible to a retro-aldol reaction to yield C_2 and C_3 compounds, which are accelerators in themselves for formose formation. The results shown above indicate that the high efficiency of HAP is a consequence of the pronounced production of glycolaldehyde, C_{3A}, and C_{3K}.

The efficiency of D-fructose in formose formation is lower than that of HAP.[3] The product distributions for the reaction accelerated by HAP and D-fructose are expected to be different in the production of lower carbohydrates. The product distributions for the HAP-accelerated reaction are illustrated in Fig. 5, while

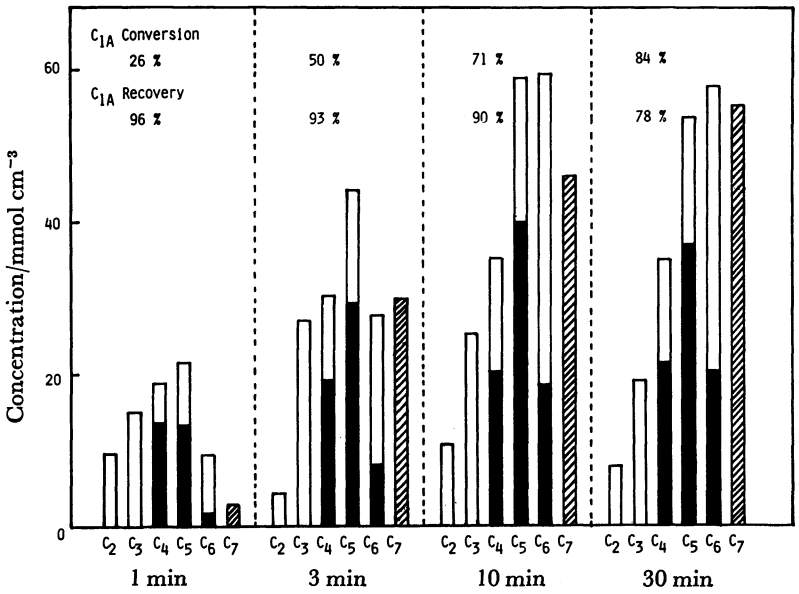


Fig. 5. C-number distributions in amounts of formose sugars and sugar alcohols obtained in the reaction accelerated by HAP. Reaction conditions; same as indicated in Fig. 2. C_n represents formose sugars and sugar alcohols having n carbon atoms. ■ or □ denotes branched chain or straight chain carbon skeleton, respectively.

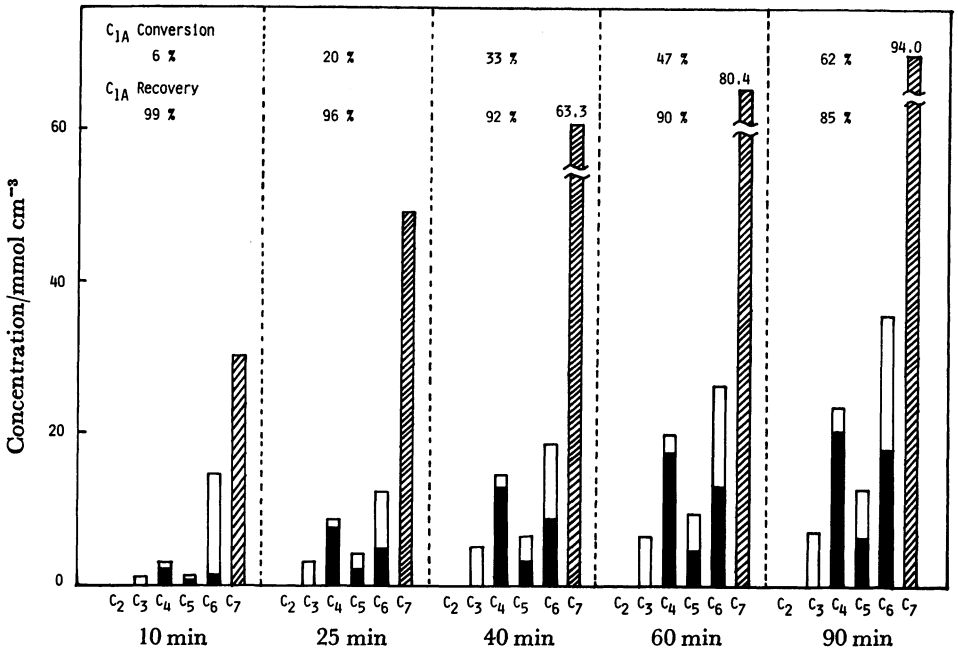


Fig. 6. C-number distributions in amounts of formose sugars and sugar alcohols obtained in the reaction accelerated by D-fructose. 45 °C, water, NaOH; 0.20 mol cm^{-3}, $CaCl_2$; 0.10 mmol cm^{-3}, C_{1A}; 2.0 mmol cm^{-3}, D-fructose; 0.05 mmol cm^{-3}.

analogous distributions for the fructose-accelerated reaction are illustrated in Fig. 6. These are determined from the GL chromatograms; therefore, the amount of C_{2A} is likely to have been evaluated too low as a result of evaporation loss during pretreatment. The amounts of C_2 and C_3 carbohydrates for the HAP-accelerated reaction are larger than those for the fructose-accelerated reaction. Moreover, the predominant carbohydrates for the fructose-accelerated reaction are aldo- and keto-heptuloses, which were presumably produced by the aldol addition of C_{1A} to D-fructose. The low efficiency of D-fructose is attributable to the low reactivity of D-fructose and/or heptuloses toward retro-aldol reactions.

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