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Homogeneously Catalyzed Condensation of Formaldehyde to Carbohydrates

VI. Preparation and Spectroscopic Investigation of Complexes Active in Formaldehyde Condensation[1]

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Condensation of formaldehyde (formose reaction) is catalyzed by complexes between alkaline earth metal hydroxides and carbohydrates, formed *in situ* in an autocatalytic reaction. When prepared externally and isolated, the complexes of $Ca(OH)_2$ with glucose and dihydroxyacetone show catalytic activities very similar to those of equivalent quantities of their components added separately to the reaction mixture. Spectroscopic (ESCA, ir) and gc data point to formation of a loosely structured and dynamic mixture of species, bonded as coordinated adducts (rather than discrete highly polarized compounds) between the alkaline earth metal hydroxide and carbohydrates. The sugars and Cannizzaro reaction products that form by condensation of HCHO in D_2O show no C–D bonds, indicating that the aqueous solvent does not participate in the formose reaction. Sugar formation from HCHO occurs within the complex.

INTRODUCTION

Formaldehyde undergoes condensation to a mixture of carbohydrates in the presence of alkaline earth metal hydroxides at pHs higher than 10.5. This is the formose reaction, and the mixture of carbohydrates produced is known as formose syrup. The reaction medium is alkaline, and so the Cannizzaro reaction takes place concomitantly. The background information and the state of the art are summarized in a review by Mizuno and Weiss (*1*) and in a series of papers published in this journal (*2–6*).

The kinetics of formaldehyde conversion are characterized by an induction period in which only the Cannizzaro reaction is measured. The induction period can be eliminated or shortened by addition of small amounts of carbohydrates to the reaction medium (*7*, *8*). Krylov and coworkers (*9*) observed that the formose reaction is accelerated to a small extent and the induction period is shortened greatly by addition of glycolaldehyde and glyceraldehyde, the initial products of formaldehyde condensation. Thus, it is accepted that the catalytically active species is not the hydroxide of an alkaline earth metal, but its complex with a carbohydrate. Existence of such complexes was suggested for the first time by Fujino *et al.* (*10*). Langenbeck and co-workers (*11*)

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[1] Part V is Ref. (*6*).

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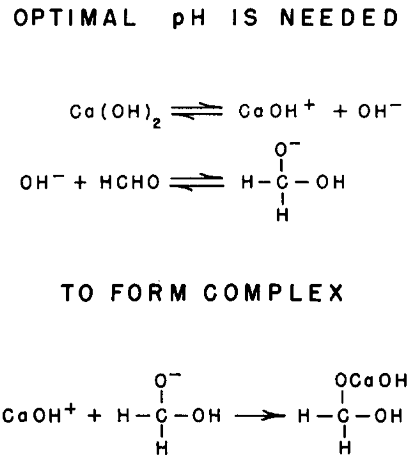


FIG. 1. Formaldehyde forms a salt-like complex with $Ca(OH)_2$. Too high or too low a hydroxyl ion concentration shifts equilibria so that either $Ca(OH)^+$ or $H_2\overset{O^-}{\overset{|}{C}}\text{–}OH$ are disfavored.

investigated the promoting effect of several compounds capable of assuming an ene-diol form. Fujino proposed the structure of the $Ca(OH)_2$–glucose complex in which the carbohydrate is complexed in its ene-diol form. Similarly, Khomenko and Krylov (*12*) assigned absorption bands in the uv-visible region, observed in solutions containing alkaline earth metal and carbohydrate, to the ene-diol structures.

On the other hand, salt-like compounds of $Ca(OH)_2$ and formaldehyde were proposed by Glotova and Irzhak (*13*). Analogous compounds of $Ca(OH)_2$ with sugars, which do not require transformation of the latter into its ene-diol form, were invoked in the reaction mechanism advanced by Weiss and John (*4*). They show data that support the idea that the complex of $Ca(OH)_2$ with formaldehyde is salt-like and is formed by the series of reactions shown in Fig. 1. This sequence excludes the participation of the solvent and is in accord with the experimentally observed pH optimum in the reaction.

The purpose of this work is to determine both the role of the solvent and the nature of the catalytically active complexes that are formed between alkaline earth metal hydroxides and carbohydrates produced after the initial complexing of HCHO. The present work includes exchange studies with D_2O during reaction, preparation of complexes in a pure form, characterization using spectroscopic techniques, and assessment of catalytic activity in the formose reaction. Preparation of complexes of carbohydrates with hydroxides (*14*) and ions (*15*) of alkaline earth metals has been investigated before, as well as the use of externally prepared complex in the formose reaction (*6*).

EXPERIMENTAL

Preparation of complexes. Complexes of alkaline earth metal hydroxides with carbohydrates were prepared following, with some modifications, the method described by Roy and Mitra (*14*). A typical procedure, illustrated here for $Ca(OH)_2$–glucose, involved adding 5 g of carbohydrate, to a suspension of 5 g of $Ca(OH)_2$ powder in 200 ml of deaerated H_2O and mixing for 1–2 hr below 15°C under argon. Undissolved $Ca(OH)_2$ was filtered off and $Ca(OH)_2$ in the supernatant solution was assayed by titration of a small aliquot. (Typically, concentrations 10–20 times higher than the solubility of $Ca(OH)_2$ in water were measured.) Next, 250–300 ml of dry acetone was added to the slightly yellow filtrate. A yellowish-white colloidal precipitate was formed. That was left overnight under a layer of acetone, filtered, and washed with 100 ml of 80% acetone followed by 100 ml of dry acetone. The solid was dried over P_2O_5 *in vacuo.* Typical yield of dry complex was 60–65%. It is possible to store the complex for a few months without apparent decomposition if it is kept in an inert gas atmosphere.

ESCA spectra of complexes were taken using an AEI ES-100 photoelectron spectrometer. The C 1s line related to the pump oil was taken as the reference (B.E. 284.6 eV). Samples of the complexes and

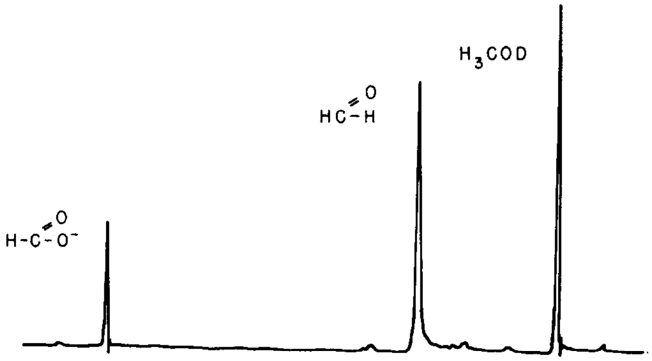


FIG. 2. NMR spectrum of Cannizzaro reaction products of HCHO and NaOD in D_2O at 30°C.

$Ca(OH)_2$ were prepared and stored under argon prior to examination. Exposure to air up to 30 min had no effect on the spectral characteristics of the $Ca(OH)_2$–glucose complex. The infrared spectra were recorded on a Carl Zeiss-Jena ir spectrometer (UR-20) in the range 400 to 4000 cm^{-1}. The solid samples were examined either as KBr tablets or as solid films deposited on ir-transparent plates. No effect of KBr on the positions of lines was noted. Spectra of D_2O solutions of complexes were obtained using a liquid cell.

Kinetics. Conversion of formaldehyde was studied at 40°C (±0.2°C) in a 250-ml jacketed and thermostated batch reactor described earlier (*5*). The initial concentration of HCHO in the reaction mixture was 1.53 *M*, unless otherwise stated, and the concentration of NaOH was 0.5 *N*. In all experiments the total volume of the reacting mixture was 100 ml. The solution of HCHO (90 ml) was brought to 40°C before a weighed amount of complex was added and allowed to dissolve. Separate experiments demonstrated that no HCHO conversion occurred at the autogeneous pH (<10.5). Ten milliliters of 5 *N* NaOH was preheated separately and added to the reaction mixture. The moment of NaOH addition was taken as the beginning of reaction. Samples of 5 ml were withdrawn at necessary time intervals and neutralized with measured amount of 1 *N* HCl in order to stop further reaction. Conversion of HCHO by Cannizzaro reaction was determined by backtitration of the acidified sample with 0.53 *N* NaOH. The total formaldehyde conversion was determined gas chromatographically (*5*) after dilution of the neutralized sample to 10 ml.

Deuterium exchange. One experiment was made to establish if deuterium from D_2O could be incorporated into the Cannizzaro products. A solution was made of 0.0071 g of paraformaldehyde in 2 ml of D_2O. To this was added 0.28 ml of a solution of 12.8 *N* NaOD in D_2O (HCHO/NaOD $=0.07$ mole/mole). The solution was monitored in the measuring cell of a Perkin–Elmer R24B NMR spectrometer at 30°C. Methanol produced was separated from the reaction mixture using a 6 ft × $\frac{1}{8}$ in. Carbosieve B column at 180°C, in a Perkin–Elmer Model 900 Dual FID chromatograph interfaced to a duPont 21-491 double-focusing electron ionization mass spectrometer. It was found that several microliters of D_2O had to be injected beforehand to deuterate the column. Otherwise a mixture of –OD and –OH is seen in the analysis of any alcohol.

To see if exchange with solvent took place with the sugar products, 13 *M* alkali solution was added to a 10:1 paraformaldehyde–$CaCl_2$ solution at 60°C. Quantities

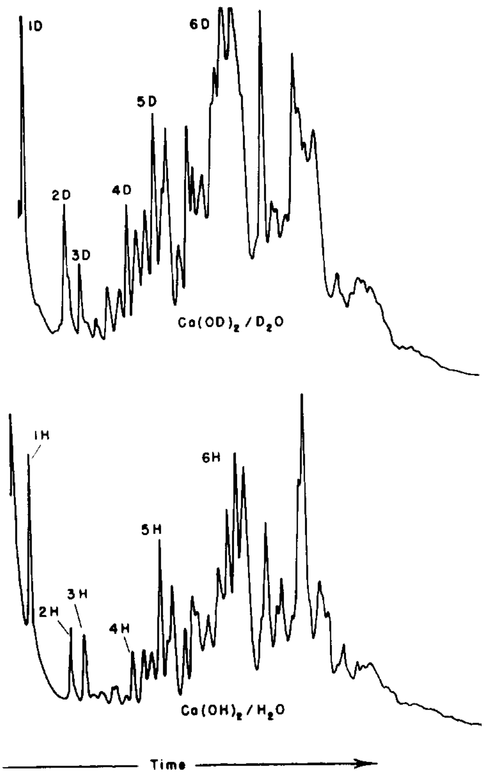


FIG. 3. Comparative chromatograms of formose sugars produced by condensation of HCHO in $Ca(OH)_2/H_2O$ and in $Ca(OD)_2/D_2O$ solutions. Mass spectral intensities of coded peaks are noted in Table 1.

are tabulated below.

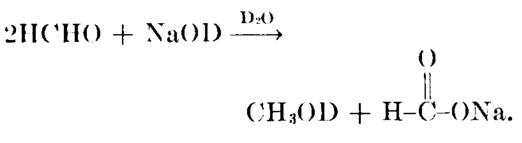
	D_2O–NaOD	H_2O–NaOH
HCHO (mmole)	6.62	6.92
$CaCl_2$ (mmole)	0.679	0.713
Solvent (ml)	4.0	4.0
Base (mmole)	1.254	1.538

Reaction was complete in 20 min. Neutralized products were freeze–dried, trimethylsilyated, and analyzed by gc–MS using the procedure described in Ref. (*2*).

RESULTS AND DISCUSSION

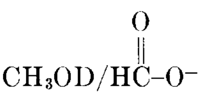
Exchange with Solvent

Figure 2 shows a typical NMR spectrum for Cannizzaro reaction proceeding in D_2O at 30°C:



$$2HCHO + NaOD \xrightarrow{D_2O} CH_3OD + H\text{–}\overset{\overset{\displaystyle O}{\|}}{C}\text{–}ONa.$$

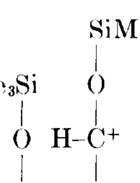
Interfaced gc-MS spectra showed that the ratio CH_3OD/CH_3OH was 80/20. Due to the large excess of D_2O, the hydroxyl group of methanol is deuterated. The heights of the



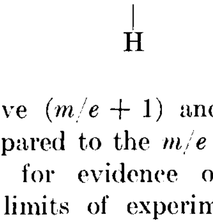
$$CH_3OD/H\overset{\overset{\displaystyle O}{\|}}{C}\text{–}O^-$$

peaks are consequently in the ratio of 3:1, but, since the scan took 5 min, NMR is not recommended to follow quantitatively the rate of the Cannizzaro reaction. Since no deuterium bonded to carbon in the products, it is clear that the aqueous solvent does not participate in the mechanism of the Cannizzaro reaction.

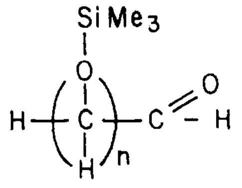
Carbohydrate product distributions for formose reaction at 60°C in D_2O and in H_2O are compared in Fig. 3. The same products were formed in somewhat (but not significantly) different proportions in D_2O and in H_2O. Mass spectra of the coded peaks in Fig. 3 were monitored at *m/e* 103,



and at *m/e* 217,



The respective (*m/e* + 1) and (*m/e* + 2) ions are compared to the *m/e* parent peak in Table 1 for evidence of exchange. Within the limits of experimental error, Table 1 shows that no deuterium was bonded to carbon atoms of the trimethylsilyl ethers of the sugars tested



(although the hydroxyl group of the parent sugar is undoubtedly deuterated in alkaline D_2O solution). Not only the Cannizzaro but also the formose mechanism for sugar formation in a $Ca(OH)_2$ complex does not involve participation of the aqueous solvent.

Activity of Complexes

Figure 4 shows that the externally prepared complexes of carbohydrates with $Ca(OH)_2$ have the same, or very similar, catalytic activities as those formed *in situ* during the reaction. The rates of HCHO conversion in the presence of $Ca(OH)_2$ (0.075 *M*) and glucose (0.072 *M*) added separately (open circles), and of the same process taking place when an equivalent quantity of the $Ca(OH)_2$–glucose complex is added to reaction mixture (filled circles) are not greatly different. At low conversion levels the two curves coincide, but after 40 min the activity of the externally prepared complex becomes somewhat higher. This might be explained in terms of decomposition of the complexed glucose to lower carbohydrates, which are known to be more active as cocatalysts of the formose process than are the original sugars. Figure 4 also shows the decrease in glucose concentration with time observed when the $Ca(OH)_2$–glucose complex is dissolved in 0.5 *N* NaOH solution at 40°C. At the moment of complete dissolution (taken here as $t = 0$) only the C_6 fraction was detected in the chromatogram of TMS derivatives of the reduced carbohydrates. The relative abundance of C_6 decreases with time while the concentrations of C_4 and C_5 fractions increase. A small amount of C_3 is also detected. Equilibrium seems to be reached after 40 min, with about

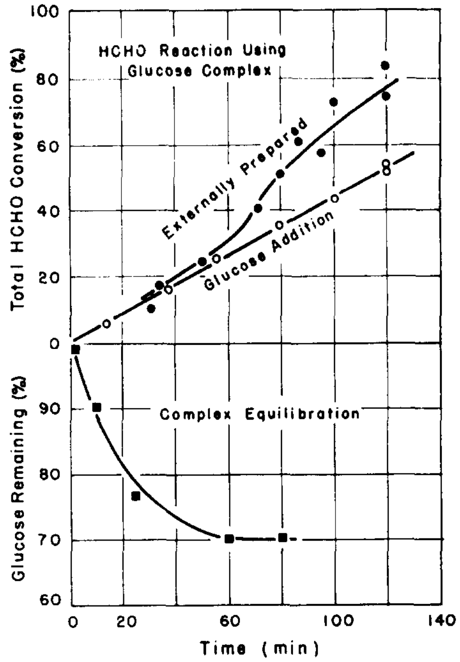


FIG. 4. Kinetics of HCHO conversion at 40°C in the presence of $Ca(OH)_2$ (0.075 *M*) and glucose (0.072 *M*) added separately (open circles), and with the equivalent amount of $Ca(OH)_2$–glucose complex (filled circles). $[HCHO]/[Ca(OH)_2] = 20$. HCHO = 1.53 *M*. Lower curve shows equilibration of $Ca(OH)_2$–glucose complex in a 0.5 *N* aqueous solution of NaOH at 40°C.

TABLE 1

Electron Ionization Fragmentation of Formose Trimethylsilyl Ethers

Fig. 3 peak No.	Peak-height ratio to $m/e = 103$[a]		Peak-height ratio to $m/e = 217$[a]	
	$m/e = 104$	$m/e = 105$	$m/e = 218$	$m/e = 219$
1 D	0.086	0.094	0.220	0.068
1 H	0.091	0.063	0.201	0.076
2 D	0.108	0.087	0.337	0.146
2 H	0.084	0.070	0.221	0.202
3 D	0.115	0.075	0.329	0.118
3 H	0.121	0.108	0.265	0.120
4 D	0.080	0.096	0.232	0.137
4 H	0.186	0.302	0.424	0.262
5 D	0.143	0.091	0.306	0.161
5 H	0.182	0.089	0.361	0.136
6 D	0.099	0.074	0.361	0.247
6 H	0.163	0.116	1.183	0.900

[a] The respective $(m/e + 1)$ and $(m/e + 2)$ ions are compared to the m/e parent peak for evidence of exchange.

30% of the glucose being converted to lower molecular weight carbohydrates. These in turn also form complexes with $Ca(OH)_2$. The dynamic nature of the formose complex was invoked from interpretations of TMS chromatograms of complexes in an earlier paper of this series (*6*). Present results strongly support the previous hypothesis that the $Ca(OH)_2$–glucose complex is not a discrete moiety, but, rather, a scrambled dynamic mixture of species. It should also be considered that peaks in the C_4 and, especially, the C_5 region might at least be partly due to the glucose isomer, saccharinic acid. The extent of this carbohydrate isomerization is currently being studied.

In spite of a very unfavorable ratio of $[HCHO]/[Ca(OH)_2]$ of 20 in 1.53 *M* HCHO, selectivity to formose products is high in the experiments shown in Fig. 4. Yield of Cannizzaro products never exceeded 15–20% at complete conversion of formaldehyde.

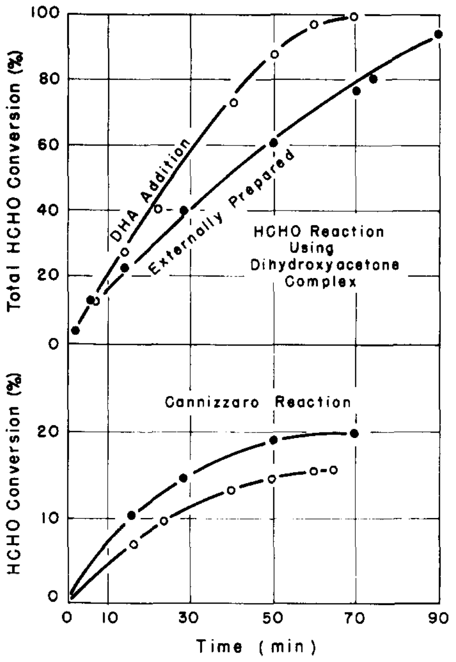


FIG. 5. Kinetics of HCHO conversion at 40°C in the presence of $Ca(OH)_2$ (0.075 *M*) and dihydroxyacetone, DHA (0.075 *M*), added separately (open circles) and with the equivalent amount of $Ca(OH)_2$–DHA complex (filled circles). $[HCHO]/[Ca(OH)_2]$ = 20. Lower curves show the corresponding conversions by the Cannizzaro reaction.

TABLE 2

Observed Binding Energies for the Ca $2p_{3/2}$ Line

Compound	Binding energy (eV)
$Ca(OH)_2$ (commercial)	346.7
$Ca(OH)_2$ (prepared under Ar)	346.7
Glucose–$Ca(OH)_2$	347.1
DHA–$Ca(OH)_2$	347.0
$CaCl_2$	347.8
CaF_2	348.3
CaO	347.3
$Ca(OOCCH_3)_2$	346.7

The activity of dihydroxyacetone (DHA) in the form of calcium complex (filled circles) is compared to the activity of equivalent amounts of $Ca(OH)_2$ and dihydroxyacetone (open circles) in Fig. 5. The rate of total HCHO conversion in the presence of the externally prepared DHA complex is lower, but not greatly different, than that observed when $Ca(OH)_2$–DHA complex is prepared *in situ*. Conversion to Cannizzaro products is also shown in Fig. 5.

Characterization of Complexes

The similarity between catalytic activities of the externally prepared complexes and complexes presumably formed *in situ* by addition to the reaction suggests that these complexes are very similar, if not identical, species. Several techniques were used in an attempt to characterize the structure of the externally prepared catalytically active complexes.

Solid complexes are amorphous to X-rays. Even prolonged exposures gave no results. But the $Ca(OH)_2$, precipitated from solution by the technique used in the preparation of complexes, yields diffraction lines identified as a mixture of $Ca(OH)_2$ and $CaCO_3$ (reaction with CO_2 from air).

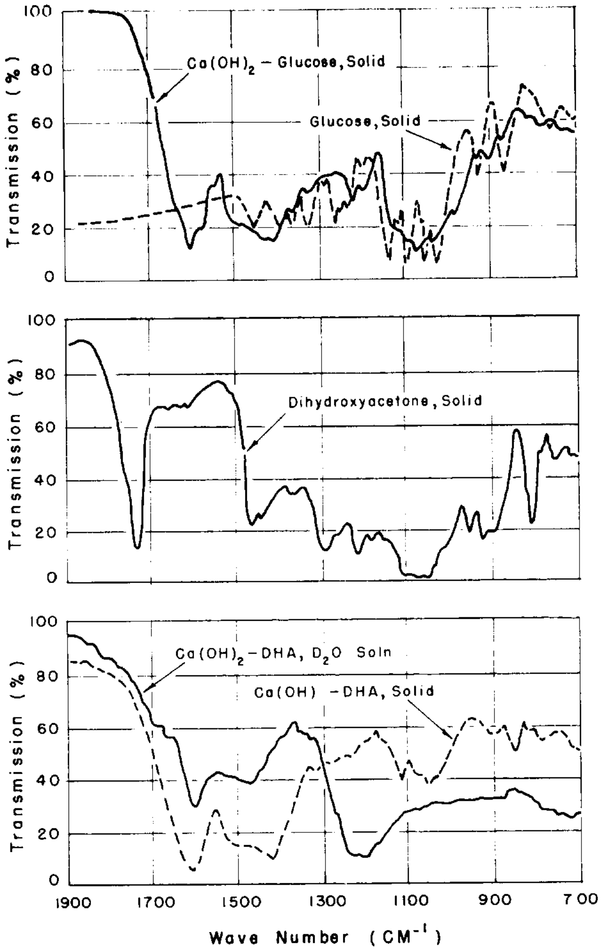


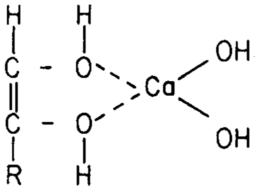
FIG. 6. Infrared spectra of glucose, DHA, and their Ca(OH)$_2$ complexes.

Thus, the preparations are not physical mixtures of Ca(OH)$_2$ and a carbohydrate.

More information was obtained from X-ray photoelectron spectra of calcium hydroxide and its complexes with glucose and dihydroxyacetone. Table 2 shows the measured values of electron binding energies for the Ca$2p_{\frac{3}{2}}$ level. For comparison data on other calcium compounds (*16*) are also shown in Table 2. Note that identical values of binding energies are observed for Ca(OH)$_2$ and calcium acetate. This is consistent with almost identical group electronegativities of the OH and acetate ligands (*17*). Large shifts in binding energy from that of Ca(OH)$_2$ in the range 0.7 to 0.9 eV are found for compounds having a calculated partial ionic character to their bonds.

A small but measurable (0.3–0.4 eV) shift is observed for both complexes with carbohydrates. There should be no shift at all from salt-like compounds, such as (OH)-Ca-(OOCCH$_3$) and, by analogy, (OH)-Ca-(carbohydrate)-(OH), due to the unchanged partial ionic character of their bonds. On the other hand formation of an adduct *via* a weakly polarized bond should result in a small observed shift [i.e., a small increase in the positive charge on Ca, compared to that existing in Ca(OH)$_2$]. Such an adduct reflects better the labile character of the active complex than a salt-like compound with strong and essentially ionic, in the case of alkali earth metals, bonds.

Fujino and co-workers (*10*) have postulated the existence of a complex in which carbohydrate in its ene-diol form is bonded to a molecule of $Ca(OH)_2$.



Obviously, this is not the only possible configuration. Other structures of complexes can be proposed which would not involve the ene-diol structure of the carbohydrate. Infrared spectra of the complexes and of carbohydrates used in their formation were recorded in order to obtain more information on complex structure.

Figure 6 shows the solid-state ir spectra of glucose (dashed line) and the $Ca(OH)_2$–glucose complex. The pyranose ring of glucose opens on complexing, and a new band appears at 1600 cm^{-1}. The spectrum of DHA is shown for comparison in Fig. 6. The carbonyl vibration in DHA is observed at 1730 cm^{-1}. The spectrum of the $Ca(OH)_2$–DHA complex is also given in Fig. 6. In the latter case the 1600-cm^{-1} band appears again, with a concomitant disappearance of the 1730-cm^{-1} band. Two explanations can be advanced: (a) shift of the carbonyl band to lower frequencies due to complexing, and (b) appearance of the C=C vibration, as required by the ene-diol structure of carbohydrate. The shift of the carbonyl band by 130 cm^{-1} is quite possible in the light of the observed position of the same band in metal complexes of acetyloacetone (*18*).

On the basis of present results we can neither prove nor dismiss the existence of the ene-diol structure of complexed carbohydrate.

Broadening and apparent structure of the 1600-cm^{-1} peak, compared to the carbonyl band at 1730 cm^{-1} makes it difficult to exclude the possibility of an overlap of two bands (namely C=0 and C=C vibrations), i.e., coexistence of two isomeric forms.

Spectra for $Ca(OH)_2$–DHA complex in D_2O solution recorded at lower frequencies (800–400 cm^{-1}) show weaker bands attributable to metal–oxygen vibrations, typical for coordination compounds, but not expected to occur in salts. Infrared spectra for $Ba(OH)_2$–DHA complexes are quite similar to those for $Ca(OH)_2$–DHA complexes.

CONCLUSIONS

Complexes of alkali earth metals with carbohydrates, similar to those postulated to be the catalytically active species, can be prepared and isolated. On the basis of ESCA and ir data it appears that they are formed by addition of one molecule of carbohydrate to $Ca(OH)_2$, forming a weakly polarized coordinated adduct. Present data are not adequate, however, to support the ene-diol structure proposed by some investigators. However, these data do confirm that the $Ca(OH)_2$–glucose complex is a dynamic and complex mixture of sugar moieties and not a discrete species. There is no great difference in activity for formose sugar preparation using as catalysts either complexes prepared *in situ* or externally. The aqueous medium does not participate in the condensation, in that no deuterium bound to carbon could be found in either the Cannizzaro products or the sugars produced by HCHO condensation in D_2O–$Ca(OD)_2$. Reaction to form sugars or CH_3OH proceeds only within the sugar or HCHO complex.

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