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ORIGINAL ARTICLE

Inhibition of cyclodextrin acid hydrolysis by some inclusion complexes

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Abstract Acidic hydrolysis of α-cyclodextrin in the solution of hydrochloric acid containing some aliphatic alcohols was investigated. The reaction was carried out at 90 °C. It was observed that the rate of the reaction has decreased with the increase in concentration of a guest.

Keywords Acidic hydrolysis · α-Cyclodextrin · Inclusion complex

Introduction

Cyclodextrins undergo hydrolysis in acidic media. The pioneering works on the investigation of this reaction were done by French [1] and Freudenberg [2] in order to examine the structure of cyclodextrins. It is known that the hydrolysis of cyclodextrin proceeds slower than the decomposition of linear oligosaccharides [3]. The data presented in the references on the rate of the hydrolysis of single cyclic glycosidic bond differs markedly. French found that the acid hydrolysis of β-cyclodextrin proceeds 5 times slower than that of linear oligosaccharides [1]. Myrback reported that it proceeds only 3 times slower [4]. The decomposition of cyclodextrins was also investigated by Szejtli and his co-workers [5, 6]. They mentioned that the formation of the inclusion complexes can slow down the rate of hydrolysis of cyclodextrins.

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It was already reported [7] that the hydrolysis of a single glycosidic bond of cyclodextrin was slower than the one of linear oligosaccharide. The rate of the reaction was found to be strongly dependent on the concentration of the catalyst (H^+ ion) (Fig. 1). It was found that reaction proceeds according to the mechanism of specific acid catalysis. That means the rate of the reactions depends only on concentration catalyst H^+ ion.

Despite the numerous studies of change of reactivity of guest molecules in the inclusion complexes little is known about the changes in hydrolysis of cyclodextrins when the guest molecule are included in the cavity. It was reported [8] that the hydrolysis of β-cyclodextrin is decelerated by some phenols and aromatic amines. Investigation of this reaction is important in order to examine the possibility of using cyclodextrins for the preparation of linear oligosaccharides [9].

Since the data about acid hydrolysis of α-cyclodextrin in presence of guest molecules are not numerous, the aim of this work was to investigate kinetics of α-cyclodextrin hydrolysis in hydrochloric acid in the presence of some aliphatic alcohols as a guest.

Experimental

α-Cyclodextrin (α-CD) containing crystallized water has been purchased from "Fluka" (Switzerland). The amount of crystallized water was taken into account during the calculations.

Hydrochloric acid (reagent grade, free from metals and higher oxidized chlorine from "Reakhim", Russia) was used for kinetic investigations. Solution of 0.1 mol dm^{-3} hydrochloric acid were prepared from ampoules. The concentration of an acid was checked titrimetrically.

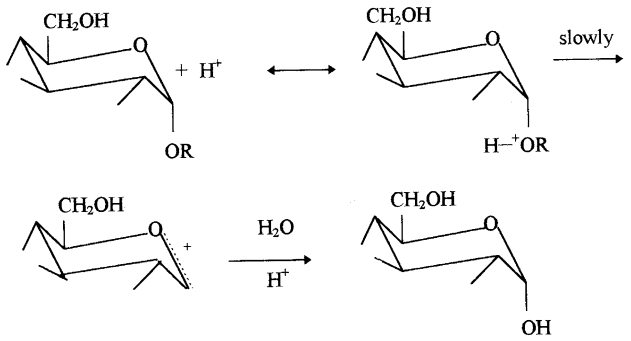

Fig. 1 Scheme of the mechanism of the acidic hydrolysis of cyclodextrin

Solutions of cyclodextrin containing 2×10^{-3} mol L^{-1} of α-CD were prepared. The concentration of a guest exceeded that of CD up to 25 fold.

The hydrolysis was carried out at 90 °C temperature in sealed vials. The range of variations of temperature did not exceed ±0.2 °C (ultrathermostate UT-10, Poland).

The kinetics of α-cyclodextrin hydrolysis was observed by fixing free carbonyl groups of oligosaccharides by Somogyj–Nelson method [10]. Linear oligosaccharides were oxidized by Cu^{2+} to Cu_2O which forms a color heteropolicomplex with Nelson reagent $Cu_3[AsMo_{12}O_{40}]$ and after that was determined colorimetrically. It was found by examination of model solutions of maltohexose and glucose ("Serva", Germany), that this method is suitable for analysis of both oligosaccharides.

Since, α-CD has no free carbonyl groups, the rate of the cycle opening (hydrolysis) can be observed by formation of the origin of such groups and may by carried out by following equation:

$$d[C]/dt = -k[C], \quad (1)$$

where k is the rate constant,

C is concentration of α-cyclodextrin.

The initial rate of reaction v_0 shows the rate opening of the cycle.

The hydrolysis was carried out in small extent (5–10% of α-CD was hydrolyzed). The kinetic curve of the reaction was extrapolated to the initial time. The first-order derivative at this point is equal to the initial rate of the reaction [11]. Then the pseudo-first order rate constant (in the presence of acid excess) was calculated according to the following equation (2):

$$k_1 = v_0/6[\alpha\text{-CD}], \quad (2)$$

where [α-CD] is the initial concentration of a host (cyclodextrin). This equation is for a single glycosidic bond, because α-CD has six such bonds. The pseudo-first order rate constant was calculated according to the following equation:

$$k_1 = k_2/[H^+]. \quad (3)$$

Hydrolysis of maltose was examined by using the enzyme methods. The concentration of the glucose formed after hydrolysis of maltose was measured using enzyme glucosoxidase.

Hydrogen peroxide produced in the reaction can be estimated amperometrically by using the oxygen electrode [12] or peroxydase [13].

Results and discussion

Bearing in mind that cyclodextrin can form inclusion complexes with compounds having hydrophobic moieties we have investigated reaction of hydrolysis of α-cyclodextrin in the presence of 1-butanol and 2-propanol as guest compounds at 90 °C in 0.1 mol L^{-1} hydrochloric acid. We observed effect of deceleration of the rate of acidic hydrolysis in both cases (see Table 1).

According to the data presented in the Table 1, when the concentration of 1-butanol exceeds the one of cyclodextrin 25 times, the rate of ring opening reaction decreased about 5 times. It is obvious that the formation of inclusion complex inhibits the rate of the reaction. Similar effect of inhibition of the reaction by the guest molecules has been observed by Uekama [8]. The reason of this effect is clear under investigation of models of cyclodextrin. The oxygen of glycosidic bond is of the internal rim of cyclodextrin cavity. Bearing in mind that the hydrolysis depends on the concentration of the catalyst (H^+ ion) it may have difficulties to attack the oxygen if the inclusion complex with the guest molecule is formed.

It was reported in number of articles that the binding abilities of cyclodextrin depends on the length of alkyl chain [14]. We also observed such effect. 1-Butanol decelerates the reaction of hydrolysis much stronger than 2-propanol. It was shown earlier that the complexation of alcohols depends on the length of the chain [15].

Table 1 Hydrolysis of α-cyclodextrin in 0.1 mol dm^{-3} hydrochloric acid at 90 °C with the presence of some alcohols

Ratio of the guest–host concentration	Pseudo-first order rate constant, $k_1 \cdot 10^{-5}$, s^{-1}	
	1-Butanol	2-Propanol
0:1	9.6 ± 1.0	9.62 ± 1.0
2.5:1	8.0 ± 0.9	8.4 ± 0.6
5:1	5.1 ± 0.5	6 ± 0.5
10:1	2.5 ± 0.3	4.1 ± 0.5
25:1	1.6 ± 0.1	3.1 ± 0.3

Investigation on reaction of hydrolysis of cyclodextrins is important for better understanding how cyclodextrins can prolong the action of some drugs. That data also could be used for the preparation technologies of manufacturing of higher oligosaccharides from cyclodextrins.

References

1. French, D., Knapp, D.W., Pazur, H.: Studies of the Schardinger dextrins. VI. The molecular size and structure of γ-dextrin. J. Am. Chem. Soc. **72**, 5120–5152 (1950)
2. Freudenberg, K.: Hydrolysis and optical rotation of cellulose, starch and glucans. J. Polym. Sci. **23**, 791–799 (1957)
3. Swanson, M., Cori, C.: Structure of polysaccharides. I. Acid hydrolysis of starchlike polysaccharides. J. Biol. Chem. **172**, 797–804 (1948)
4. Myrback, K.: Schardinger dextrins. II. Calculations of the acidic hydrolysis. Arkiv. Chem. **1**, 161–177 (1949)
5. Szejtli, J., Budai, Z.: Acid hydrolysis of β-cyclodextrin. Acta Chem. Acad. Sci. Hung. **91**, 73–80 (1978)
6. Szejtli, J.: Interaction of hydrochloric acid with cyclodextrin. Staerke/Starch **29**, 410–413 (1977)
7. Vaitkus, R., Grincienė, G., Norkus, E.: Peculiarities of β-cyclodextrin acid hydrolysis. Chemija **19**, 48–51 (2008)
8. Hirayama, F., Kurihara, M., Utsuki, T., Uekama, K.: Inhibitory effect of guest molecules on acid-catalyzed ring-opening of β-cyclodextrin. J. Chem. Soc. Chem. Commun. 1578 (1993)
9. Kondo, H., Nakatami, H., Hiromi, K.: Rapie preparation of maltooligosaccharides from cyclodextrins by column chromatography of hydrophylic vinyl polymer gel. Agric. Biol. Chem. **45**, 2369–2370 (1981)
10. Nelson, N.: A photometric adaptation of the Somogyi method for the determination of glucose. J. Biol. Chem. **153**, 375–380 (1944)
11. Dagys, R., Tumas, S., Zvirblis, S., Pauliukonis, A.: Determination of first and second derivative of progress curves in the case of unknown experimental error. Comput. Biomed. Res. **23**, 490–498 (1990)
12. Vaitkus, R., Griškonis, E.: Investigation of some thermodynamic parameters of acidic hydrolysis ß-cyclodextrin in the presence of inclusion complexes. Org. React. (Tartu) **31**, 27–31 (1997)
13. Kulys, J.: Analytical Systems Basing on Immobilised Enzymes, pp. 1–200. Mokslas, Vilnius (1981)
14. Inoue, Y., Okuda, T., Miyata, Y., Chujo, R.: NMR studies of cycloamylose inclusion complexes with p-substituted phenols. Carbohydr. Res. **125**, 65–76 (1984)
15. Spencer, J.N., DeGarmo, J., Paul, I.M., He, Q., Ke, X., Wu, Z., Yoder, C.H., Chen, Sh., Mihalick, J.E.: Inclusion complexes of alcohols with α-cyclodextrin. J. Sol. Chem. **24**, 601–609 (1995)