Kinetic aspects of the reaction of succinoylated dextran with glycidyl acetate

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This work deals with the reaction of succinoylated dextran with glycidyl acetate (a model compound of glycidyl bioactive derivative) using benzyltriethylammonium chloride as catalyst. The reaction shows second order kinetics and depends on the glycidyl acetate and catalyst concentrations, showing no dependence on the acid groups' concentration. On the basis of these findings a probable mechanism of the reaction is suggested.

(Keywords: succinoylated dextran; glycidyl acetate; model compound; β-hydroxyester groups; mechanism of reaction)

INTRODUCTION

A number of polymeric esters of biologically active carboxylic acids have been prepared by reacting such bioactive compounds with polymers containing epoxy groups linked to the main chain[1–3]. An alternative method of obtaining such polymeric derivatives was developed by Brosse *et al.*[4] in which the epoxy group is linked to the active carboxylic acid.

On the other hand, the functionalization of dextran with carboxylic acid groups by reaction with succinic anhydride[5] provides the possibility of obtaining polymer-bioactive compound adducts by reacting the succinoylated dextran with glycidyl derivatives of bioactive carboxylic acids.

This paper describes a study of the kinetic aspects of the reaction of succinoylated dextran with glycidyl acetate, a model compound for glycidyl bioactive derivatives.

EXPERIMENTAL

Materials

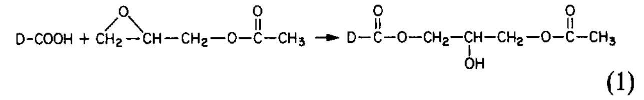
The succinoylated dextran was obtained as described earlier[5]. Dextran (18 g, 0.33 mol OH, T-70 from Pharmacia Fine Chemical) was reacted at 80°C with succinic anhydride (33.5 g, 0.33 mol, Ferosa) using 900 ml of *N*,*N*-dimethylformamide (DMF, Ferosa) containing 2 g of LiCl/100 ml as solvent and 26 g (0.33 mol) of pyridine (Panreac) as catalyst. The reaction time was 30 h and the polymer was isolated by precipitating in cold 2 M hydrochloric acid, washing with ice-cold water, dissolving in $NaHCO_3$ solution, precipitating the sodium salt in acetone, dissolving the polymer in water, reprecipitating in 2 M hydrochloric acid, washing with ice-cold water, dissolving in acetone and finally precipitating in diethyl ether. The modified polymer was characterized by i.r. and ^1H and ^{13}C n.m.r. The degree of substitution (*DS*) was determined by titration of the polymer in dimethyl sulfoxide (DMSO) solution with 0.1 M sodium hydroxide in the presence of phenolphthalein. The polymer contained 72.0 mol% of ester groups ($DS = 2.16$). Glycidyl acetate was synthesized by reaction of acetyl chloride with 2,3-epoxy-1-propanol following an established method[6].

Reaction of succinoylated dextran with glycidyl acetate

Succinoylated dextran ($DS = 2.16$) was dissolved in DMF in a double-walled reactor. The calculated amounts of catalyst (benzyltriethylammonium chloride) and glycidyl acetate were added while stirring. All the reactions were performed at constant temperature and the polymer remained soluble throughout the process. The extent of reaction was followed by sampling the reactant solution, taking aliquot parts at definite periods of time, and titrating the acid groups against 0.1 M sodium hydroxide using phenolphthalein as indicator. Characterization of the modified polymers was carried out by ^1H n.m.r. spectroscopy using a 200 MHz Bruker AM-200 spectrometer.

RESULTS AND DISCUSSION

Preliminary experiments have shown that in the reaction of succinoylated dextran with glycidyl acetate at 85°C in DMF, the polymer is practically unchanged in the absence of catalyst. However, when a catalyst is utilized, polymers containing β-hydroxyester groups were obtained, according to the following scheme:



(1)

where D–COOH = succinoylated dextran.

The assignments and ^1H n.m.r. chemical shifts of the different hydrogen atoms for modified dextran containing β-hydroxyester groups as well as for succinoylated dextran and glycidyl acetate are summarized in *Table 1*.

In general, reactions of epoxides with carboxylic acids

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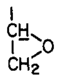
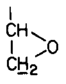
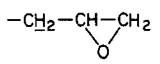
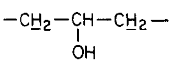
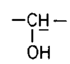
Table 1 ^{1}H n.m.r. signals[a] for modified dextran containing β-hydroxyester groups as well as for succinoylated dextran and glycidyl acetate

Compound	 $\mathrm{D{-}\overset{O}{\overset{\|}{C}}{-}(\underline{CH_2})_2{-}}$				 $\mathrm{{-}\underline{CH_2}{-}\underset{OH}{\underset{\mid}{\underline{C}H}}{-}\underline{CH_2}{-}}$	 $\mathrm{{-}\underset{OH}{\underset{\mid}{\underline{CH}}}{-}}$	$\mathrm{{-}\underline{CH_3}}$
Glycidyl acetate	–	3.1	2.6 2.7	3.8 4.3	–	–	2.0
Succinoylated dextran	2.9	–	–	–	–	–	–
Modified dextran containing β-hydroxyester groups	2.8 2.9	–	–	–	4.1	3.4	2.0

[a] Measured in chloroform (100 mg ml^{-1})

Table 2 Degree of modification in the reaction of succinoylated dextran with glycidyl acetate in the presence of various catalysts[a]

Catalyst	Time (h)	Degree of modification (mol%)
Pyridine[b]	5.5	11.5
	22.0	43.9
4-Dimethylamine pyridine[b]	5.5	26.0
	22.0	67.0
Benzyltriethylammonium chloride[b]	5.5	40.0
	22.0	78.7
Benzyltriethylammonium chloride[c]	5.5	25.0
	22.0	48.5
Salt of tetramethylammonium of succinoylated dextran[c]	5.5	18.2
	22.0	51.3

[a] Solvent DMF (25 ml), temperature 85°C, [acid] 0.23 mol l^{-1}, [epoxide] 0.23 mol l^{-1}

[b] [Catalyst] 0.044 mol l^{-1}

[c] [Catalyst] 0.022 mol l^{-1}

Table 3 Reaction of succinoylated dextran ([acid] = 0.128 mol l^{-1}) with glycidyl acetate ([epoxide] = 0.128 mol l^{-1}) under stoichiometric conditions using DMF as solvent and benzyltriethylammonium chloride as catalyst

Experiment no.	[catalyst] (mol l^{-1})	Temperature (°C)	$k_1 \times 10^5$ (s^{-1})
1	0.040	65	0.4
2	0.040	75	0.7
3	0.040	85	1.8
4	0.040	95	3.5
5	0.020	85	0.8
6	0.030	85	1.4
7	0.061	85	2.9

are catalysed either by tertiary amines or quaternary ammonium salts[7]. *Table 2* shows the influence of the catalyst on the degree of modification in the reaction of succinoylated dextran with glycidyl acetate in DMF.

Table 3 shows the experimental conditions for the reaction of succinoylated dextran with glycidyl acetate at stoichiometry using benzyltriethylammonium chloride as catalyst. *Figure 1* shows the kinetic results for this reaction at various temperatures. The progress of the reaction was followed by carboxyl group titration[8]. We consider that under our experimental conditions, the carboxy and the epoxy groups disappear at the same rate as was proposed by Madec and Maréchal[8] in other carboxy–epoxy reactions.

Figure 2 represents the dependence of ln$[\mathrm{A}]_0/[\mathrm{A}]$ ($[\mathrm{A}]_0$ is initial acid concentration, [A] is acid concentration at time t) on time from the experimental data of *Figure 1*. From the results reported in *Figure 2*, it appears that the global order in reactants is one. This is in good agreement with the behaviour found for other reactions catalysed by quaternary ammonium salts[9–12]. The straight lines do not pass through the origin and the ordinate value does

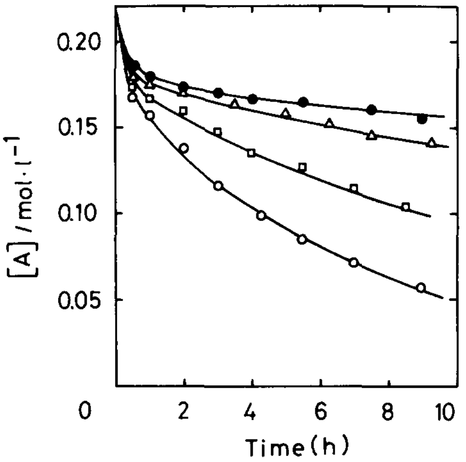


Figure 1 Dependence of [A] (acid concentration at time t) on time for the reaction of succinoylated dextran ([acid] = 0.218 mol l^{-1}) with glycidyl acetate ([epoxide] = 0.218 mol l^{-1}) using benzyltriethylammonium chloride as catalyst (0.040 mol l^{-1}) at various temperatures: ○, 95°C; △, 85°C; □, 75°C; ●, 65°C

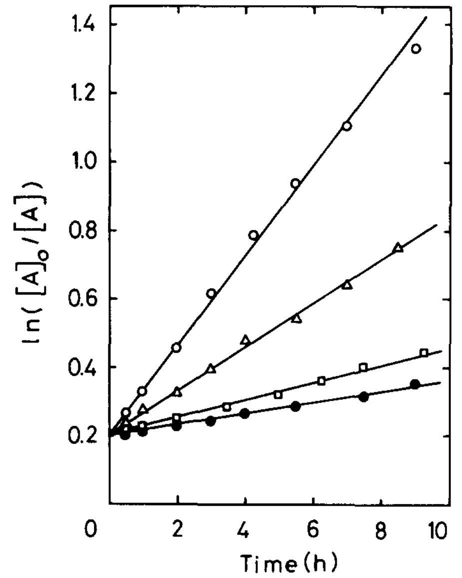


Figure 2 First order plots ($[\mathrm{A}]_0$ = initial acid concentration) for the reaction of succinoylated dextran ([acid] = 0.218 mol l^{-1}) with glycidyl acetate ([epoxide] = 0.218 mol l^{-1}) using benzyltriethylammonium chloride as catalyst (0.040 mol l^{-1}) at various temperatures: ○, 95°C; △, 85°C; □, 75°C; ●, 65°C

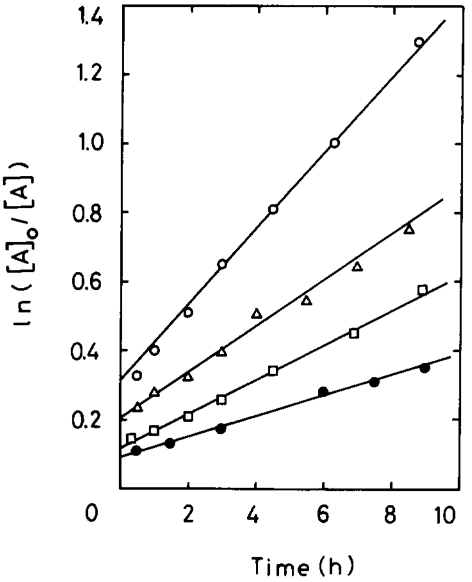


Figure 3 First order plots for the reaction of succinoylated dextran ([acid] = 0.218 mol l^{-1}) with glycidyl acetate ([epoxide] = 0.218 mol l^{-1}) at 85°C using benzyltriethylammonium chloride as catalyst. [Catalyst]: ●, 0.020 mol l^{-1}; □, 0.030 mol l^{-1}; △, 0.040 mol l^{-1}; ○, 0.061 mol l^{-1}

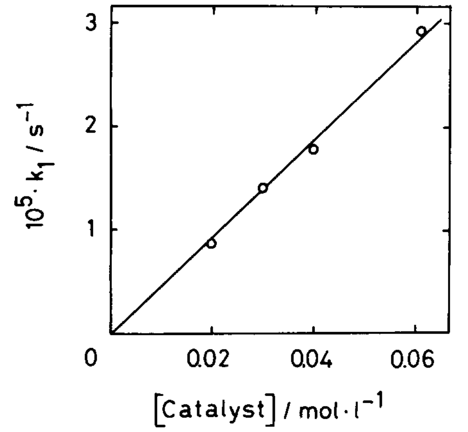


Figure 4 Plot of rate constant k_1 *versus* [catalyst] for the reaction of succinoylated dextran ([acid] = 0.218 mol l^{-1}) with glycidyl acetate ([epoxide] = 0.218 mol l^{-1}) at 85°C using benzyltriethylammonium chloride as catalyst

not depend on the reaction temperature. This behaviour was also observed in the reaction of glycidyl derivatives with palmitic acid using quaternary ammonium salts[9,10], a result due to the complex mechanism of the reaction, as will be discussed below. Rate constants (k_1) of these reactions are reported in *Table 3*.

Figure 3 represents the dependence of $\ln[A]_0/[A]$ on time at various catalyst concentrations using stoichiometric concentrations of reactants. The ordinate value increases with increasing benzyltriethylammonium chloride concentration. From the slope of each straight line we determined the values of the rate constant k_1 (*Table 3*).

From the dependence of k_1 on the catalyst concentration (*Figure 4*) it can be concluded that the order in catalyst is one.

Figures 5 and *6* show kinetic results for the reaction of succinoylated dextran with glycidyl acetate when the reaction is carried out under non-stoichiometric conditions (*Table 4*). From inspection of *Figure 5*, the conclusion reached is that the reaction rate depends on the concentration of glycidyl acetate. The plot of $\ln[E]_0/[E]$ ($[E]_0$ and $[E]$ are the concentrations of epoxy groups initially and at time t, respectively) *versus* time, from experimental data of *Figure 5*, gives straight lines in all cases. These results make it clear that the reaction rate is of first order with respect to the epoxy concentration. It may be noticed that the straight lines

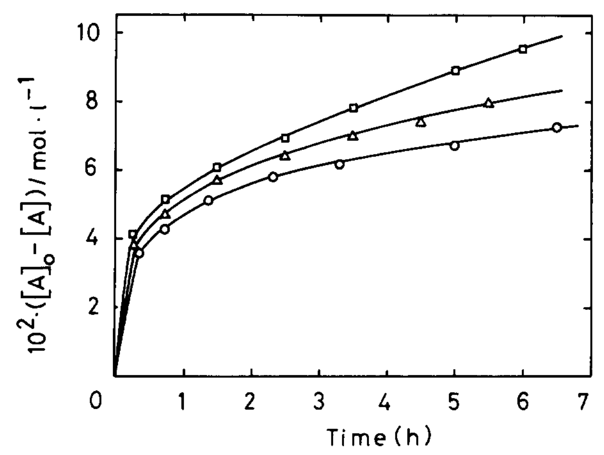


Figure 5 Reaction of succinoylated dextran ([acid] = 0.218 mol l^{-1}) with glycidyl acetate under non-stoichiometric conditions using benzyltriethylammonium chloride (0.043 mol l^{-1}) as catalyst. [Epoxide]: ○, 0.108 mol l^{-1}; △, 0.143 mol l^{-1}; □, 0.177 mol l^{-1}

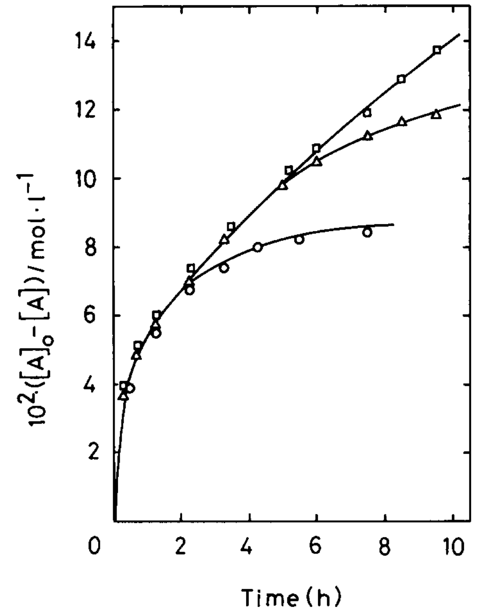


Figure 6 Reaction of succinoylated dextran with glycidyl acetate ([epoxide] = 0.218 mol l^{-1}) under non-stoichiometric conditions using benzyltriethylammonium chloride (0.043 mol l^{-1}) as catalyst. [Acid]: ○, 0.081 mol l^{-1}; △, 0.117 mol l^{-1}; □, 0.157 mol l^{-1}

Table 4 Reaction of succinoylated dextran with glycidyl acetate under non-stoichiometric conditions using DMF as solvent and benzyltriethylammonium chloride as catalyst (4.3×10^{-2} mol l^{-1}) at 85°C

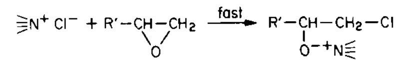
Experiment no.	$[\mathrm{acid}]_0$ (mol l^{-1})	$[\mathrm{epoxide}]_0$ (mol l^{-1})	$k_1 \times 10^5$ (s^{-1})
8	0.218	0.108	2.1
9	0.218	0.143	2.0
10	0.218	0.177	2.0
11	0.081	0.218	1.9
12	0.117	0.218	2.0
13	0.157	0.218	2.0

do not pass through the origin and the ordinate value increases with decreasing initial glycidyl acetate concentration.

On the other hand, as can be seen from *Figure 6*, the reaction rate does not depend on the acid groups concentration. This was in good agreement with an order zero with respect to acid groups. We observed that when a certain degree of modification was reached, a negative deviation in the kinetic curves was observed, which depends on the acid concentration used. This behaviour is probably related to the mechanism of the reaction. The plot of $\ln[E]_0/[E]$ *versus* time, from experimental data of *Figure 6*, also gives straight lines which do not pass through the origin. All straight lines show the same ordinate value.

It was observed (*Table 4*) that the rate constant k_1 obtained under non-stoichiometric conditions exhibits virtually the same value.

According to the kinetic results reported in this work, the order of reaction with respect to acid, epoxy and catalyst is zero, one and one, respectively, in the reaction of succinoylated dextran with glycidyl acetate catalysed by benzyltriethylammonium chloride. The above findings can be explained by assuming a mechanism similar to that proposed by Shvets *et al.*[12] for the reaction of carboxylic acids with ethylene oxide using tetraalkylammonium halides as catalysts. According to this mechanism, the reaction process involves the following steps: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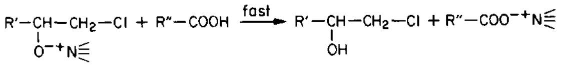
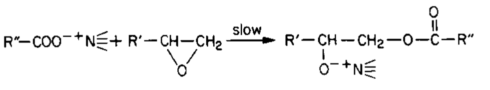
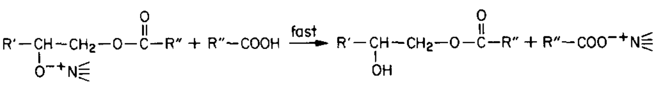


$$\underset{\substack{|\\ O^{-}\,{}^{+}N\lessgtr}}{R'\!-\!CH}\!-\!CH_2\!-\!Cl + R''\!-\!COOH \xrightarrow{fast} \underset{\substack{|\\ OH}}{R'\!-\!CH}\!-\!CH_2\!-\!Cl + R''\!-\!COO^{-}\,{}^{+}N\lessgtr \tag{3}$$


(4)



$$\underset{\substack{|\\ O^{-}\,{}^{+}N\lessgtr}}{R'\!-\!CH}\!-\!CH_2\!-\!O\!-\!\overset{\substack{O\\ \|}}{C}\!-\!R'' + R''\!-\!COOH \xrightarrow{fast} \underset{\substack{|\\ OH}}{R'\!-\!CH}\!-\!CH_2\!-\!O\!-\!\overset{\substack{O\\ \|}}{C}\!-\!R'' + R''\!-\!COO^{-}\,{}^{+}N\lessgtr \tag{5}$$

In the mechanism under discussion we have considered the assumption that the total amount of benzyltriethylammonium chloride reacts with glycidyl acetate at the very beginning of the reaction, giving rise to halohydrin derivative and benzyltriethylammonium carboxylate (equations (2) and (3)). The carboxylate ion formed participates in the mechanism as a catalytic species in the following reaction step (equation (4)). The catalytic species, $R''\text{-}COO^{-}\,{}^{+}N\lessgtr$, is immediately regenerated according to equation (5). The rate-determining step is the reaction of the carboxylate ion with epoxy groups (equation (4)).

From equations (4) and (5) it follows:

$$\underset{c}{R''\!-\!COO^{-}\,{}^{+}N\lessgtr} + \underset{b-c-x}{\text{epoxide}} \xrightarrow{\text{acid}} \underset{x}{\text{ester}} + \underset{c}{R''\!-\!COO^{-}\,{}^{+}N\lessgtr} \tag{6}$$

and

$$\frac{dx}{dt} = kc(b-c-x) \tag{7}$$

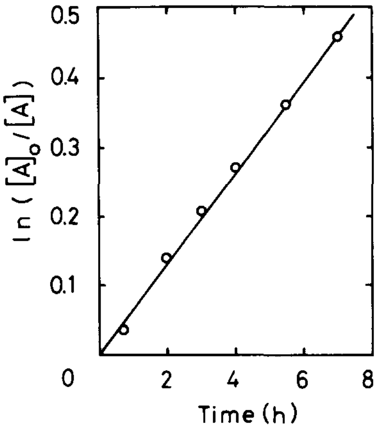


Figure 7 First order plot for the reaction of succinoylated dextran ([acid] = 0.218 mol l^{-1}) with glycidyl acetate ([epoxide] = 0.218 mol l^{-1}) at 85°C using tetramethylammonium salt of succinoylated dextran as catalyst ([salt] = 0.040 mol l^{-1})

where $x = \beta$-hydroxyester concentration at time t, c = carboxylate ion concentration = initial concentration of benzyltriethylammonium chloride, and b = initial concentration of glycidyl acetate.

The integrated form of equation (7) is:

$$\ln\frac{b-c}{b-c-x} = kct \tag{8}$$

which is equivalent to:

$$\ln\frac{[E]_0}{[E]} = kct - \ln\left(1-\frac{c}{b}\right) \tag{9}$$

According to equation (9), the plot of $\ln[E]_0/[E]$ *versus* time gives straight lines which do not pass through the origin, in accordance with the experimental results. In all cases, the ordinate values calculated from equation (9) are in good agreement with the experimental ordinate values.

The observed deviation in reaction rate in *Figure 6* may be attributed to a decrease of the concentration of carboxylate ions as a consequence of the depletion of the acid groups, which prevents regeneration of the carboxylate groups.

The proposed mechanism of reaction was further checked by using a tetramethylammonium salt of succinoylated dextran as catalyst, which was prepared by partial neutralization with tetramethylammonium hydroxide. In this case, the dependence of $\ln[A]_0/[A]$ on time (*Figure 7*) gives a straight line which passes through the origin ($k_1 = 1.9\times10^{-5}\,s^{-1}$).

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