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The Kinetics of Solid-State Catalytic Tritiation of Thymine

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This is a kinetic study of the reactions occurring in the thymine/Pt black/tritium–protium system in the temperature range of −25–70°C. The following parallel reactions occur in the system: hydrogenation of thymine into dihydrothymine, isotopic substitution producing [^{3}H]thymine, and hydrogenation of [^{3}H]thymine into dihydrothymine. The ratio of dihydrothymine to [^{3}H]thymine grows many times as the reaction rate rapidly decreases, the growth rate being the highest at the onset of the reaction. The results are in qualitative and quantitative agreement with the diffusion model of solid-state catalytic hydrogenation proposed earlier. © 1991 Academic Press, Inc.

INTRODUCTION

The reaction of solid-state catalytic hydrogenation (SSCH) was first observed (*1*) in the formation of tungsten bronzes at room temperature from a mechanical mixture of WO_3 and Pt/Al_2O_3. In the literature one finds a number of works on the SSCH of inorganic compounds, mostly the reduction of metal oxides. SSCH is based on hydrogen spillover, i.e., the penetration of activated hydrogen from the metal catalyst surface into the compound phase. There is a number of reviews of works on hydrogen spillover and the SSCH of inorganic compounds (*2–5*). The possible role in the SSCH of co-catalysts such as water or other proton acceptors is discussed (*6*). Il'chenko (*5*) sums up what seem to be the general laws of the solid-state catalytic reduction of metal oxides:

(i) The accelerating effect of the metal catalyst is the greater the closer the contact between its microcrystals and the oxide surface. For example, if platinum is applied to tungsten anhydride through impregnation, the reduction rate is higher than that on grinding with platinum black, and much higher than that with simple shaking of a mixture of platinum and oxide powder.

(ii) The catalytic effect of metal catalyst additions (very small amounts) is proportional to the metal concentration: at high enough concentrations one observes the saturation effect: any further addition of metal has little effect on the reduction rate. For example, the reduction of vanadium oxides is accelerated by trace amounts of platinum (0.0005%), while saturation occurs at the platinum content of 0.25%.

SSCH of Organic Compounds

The SSCH of organic compounds was described (*7*). SSCH offers some new opportunities for synthesis of tritium-labeled organic compounds (*7*). SSCH could accomplish the asymmetric hydrogenation of an achiral compound with an achiral catalyst using the chirality of the crystalline packing alone (*8*). An investigation has been made (*9*) concerning the effects of the procedure used for preparing the reaction mix (thymine/Pt black) on the conversion of the initial reagent: the greatest conversion has been shown to occur after Pt black had been mixed with thymine powder prepared from a lyophilized solution. As to the effects of the amount of catalyst in the reaction mix on the reagent's conversion (*9*), the relation here is qualitatively similar to the metal oxide reduction situation: direct proportionality for small

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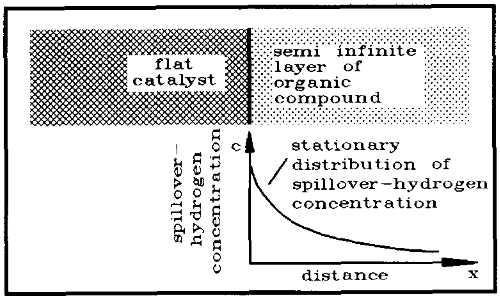


FIG. 1. The reaction system scheme considered in the diffusion model.

amounts of the catalyst and a saturation effect for large enough amounts.

The diffusion model for the SSCH has been proposed (*10, 11*). The chief assumption of this model is that in the organic compound phase there is a concentration gradient of spillover hydrogen resulting from diffusion and from reactions with the organic compound, and this gradient determines the reaction kinetics. This very assumption provides some consequences of qualitative character (and also for the reaction kinetics) that cannot be obtained without it. In addition, to infer formulae obtained in those papers, some other simplifying assumptions were made:

(i) Spillover hydrogen particles disappear in the hydrogen exchange reaction with organic compound (the exchange with labile as well as nonlabile H atoms); all other reactions (recombination, hydrogenation) do not contribute considerably.

(ii) The hydrogenation reaction proceeds with a stationary distribution of spillover hydrogen in the organic compound phase (Fig. 1).

(iii) The organic phase is a semi-infinite layer adjacent to the flat catalyst (Fig. 1).

This model gives the following kinetic equation for the quantity of the reaction product $Q_{\mathrm{product}}(t)$:

$$Q_{\mathrm{product}}(t) = b\int_0^1 [1 - \exp(-aty)]y^{-1}dy = b\sum_{n=1}^{\infty}\frac{(-1)^{n-1}}{n(n!)}(at)^n, \quad (1)$$

where $a = k_{\mathrm{P}}I\,(kD[R\mathrm{H}]_0)^{-0.5}$, $b = S(D[R\mathrm{H}]_0/k)^{0.5}$; k_{P} is the rate constant of product formation, I is the flux of spillover hydrogen into the organic phase, k is the summated rate constants of reactions destroying spillover hydrogen, D is the diffusion coefficient, $[R\mathrm{H}]_0$ is the initial organic compound concentration, and S is the catalyst/organic compound interface area. The integration variable y is the result of substitution of variables, and it is related to the initial variable x (the distance from the catalyst surface deep into the organic phase) by the formula

$$y = \exp[-x(k/D)^{1/2}].$$

This equation is applicable to the early stage of the reaction when the conversion of the original compound is $\leqslant 100\%$.

The real reaction system consists of the catalyst particles mixed with particles of the organic compound. In a similar system, spillover includes not only penetration through the catalyst/compound interface and diffusion in the volume of the organic compound, but also the diffusion through interfaces of organic particles and, possibly, the diffusion over the surface of organic particles. Therefore, I and S, in terms of this reaction system, will denote some effective values. Although the assumptions, in which the equations of the diffusion model are inferred, greatly coarsen the real situation, one may, however, hope that the obtained equations will describe the experimental kinetics as a satisfactory agreement of Eq. (1) to one set of experimental data has already been shown (*11*).

SSCH models assuming the reaction kinetics to be determined by catalyst poisoning have also been proposed (*10, 11*). The following mechanisms of catalyst poisoning are discussed in these works:

(i) Catalyst surface poisoning by the product of the reaction between H atoms and the original compound;

(ii) catalyst surface poisoning by the product of the reaction between H atoms and a contamination layer adsorbed on the catalyst surface;

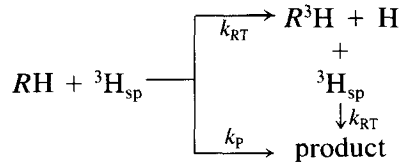
(iii) passivation of the catalyst surface by chemisorbed hydrogen. Depending on the nature of assumptions regarding intermediate stages, they produced the following kinetic equations:

$$Q_{\text{product}}(t) = b[1 - \exp(-at)] \qquad (2)$$

$$Q_{\text{product}}(t) = b\tanh(at). \qquad (3)$$

Here a and b have meanings different than those in Eq. (1). The plot of function (1) has a shape different enough from the plots of functions (2) and (3) for the regression of experimental data by these equations to establish which model is capable of describing the experiment.

Interesting results follow from the diffusion model for systems with parallel isotope exchange and hydrogenation reactions:



$$RH + {}^3H_{sp} \xrightarrow{k_{RT}} R^3H + H \quad ; \quad H + {}^3H_{sp} \xrightarrow{k_{RT}} \text{product} \quad ; \quad RH + {}^3H_{sp} \xrightarrow{k_P} \text{product} \qquad (4)$$

where RH is the initial compound, ${}^3H_{sp}$ is an atom of spillover-tritium (all results apply to deuterium as well). For this system the beginning of the reaction (initial reagent conversion $\ll 100\%$) is described by the equations, in accordance with the diffusion model,

$$Q_{RT}(t) = b\int_0^1 \exp(-a_P tz)[1 - \exp(-a_{RT}tz)]z^{-1}\,dz \qquad (5)$$

$$Q_{\text{product}}(t) = b\int_0^1 [1 - \exp(-a_P ty)]y^{-1}\,dy \qquad (6)$$

$$Q_{RT}(t) + Q_{\text{product}}(t) = b\int_0^1 \{1 - \exp[-(a_{RT} + a_P)ty]\}y^{-1}\,dy, \qquad (7)$$

where $a_{RT,P} = k_{RT,P}/(kD[RH]_0)^{-0.5}$, Q_{RT} and Q_{product} are amounts of tritiated original compound and hydrogenation product, respectively, and b has the same meaning as in Eq. (1). The reaction kinetics in such a system is characterized by the following feature:

the ratio of hydrogenation products and isotope exchange products grows many times while the reaction rate rapidly drops, the growth rate being maximum at the initial moment.

This qualitative characteristic follows from the diffusion model major assumption that the reaction kinetics is determined by the spillover hydrogen concentration gradient in the organic phase. No other models can provide these qualitative effects, as in case the basic assumption of the diffusion model is not valid (i.e., if the spillover hydrogen gradient has no considerable effect on the reaction kinetics) this ratio obviously cannot increase from the onset of the reaction: its increase can become appreciable only when a decrease of the initial compound concentration becomes appreciable.

The qualitative prediction of the diffusion model that we described may be therefore regarded as *a means of the identification of the reaction mechanism.* If we have experimentally obtained the result mentioned (a repeated and monotonously slowing growth of the products' concentration ratio), we can state that the kinetics of the reaction is determined by the spillover-hydrogen gradient in the organic phase.

The investigation of a system with parallel reactions (4) is of interest for one more reason. The presence of crystal environment prevents the formation of some hydrogenation products yielded in the reaction in solution (*8*). It is evident that reactions can exist that are only limited and not prevented by crystal surroundings. In this case it is evident that by lowering the temperature it is possible to "suppress" the reaction against the background of isotopic exchange. This problem is of practical interest for the production of hydrogen isotope-labeled compounds.

The objectives of this work were to conduct an experimental study of the kinetics of solid-state catalytic tritiation of thymine

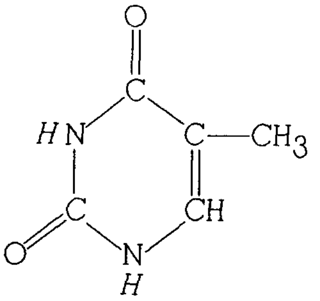


FIG. 2. The structural formula of the thymine molecule. Italic letters denote labile hydrogen atoms.

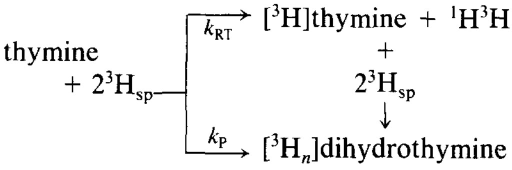
in the −25°–70°C temperature range, and to choose a model for an adequate description of the results and the plotting of temperature dependences for the kinetic equation parameters and for the ratio of hydrogenation and isotope exchange rate constants.

METHODS

Platinum black was obtained as described (*13*). The reaction mixture was prepared by mixing Pt black with thymine powder, obtained by lyophilic drying of solution (i.e., drying the frozen solution in forevacuum), in the 15 : 1 proportion (g/g). The structural formula of thymine showing labile and stable H atoms is presented in Fig. 2. The reaction was carried out with an admixture of hydrogen–tritium 1000 : 1 at 60 Torr (1 Torr = 133.3 $N\ m^{-2}$). Labile radioactivity was removed by isotopic exchange with water, followed by lyophilization. Nonlabile radioactivity was measured by a liquid scintillation counter. The relative standard deviation (the coefficient of variation) of total product radioactivity measurements was 25%. Reaction products were analyzed by thin-layer radiochromatography on cellulose plates in *t*-butanol : methyl ethyl ketone : ammonium hydroxide : water (40 : 30 : 20 : 10 ml). Ninety to ninety-five percent of the radioactivity was contained in thymine and dihydrothymine.

RESULTS AND DISCUSSION

We have studied the tritiation of thymine:



$$\begin{array}{ll} & \xrightarrow{k_{RT}} [{}^3H]\text{thymine} + {}^1H^3H \\ \text{thymine} & \qquad\qquad + \\ \quad + 2{}^3H_{sp} & \qquad\quad 2{}^3H_{sp} \\ & \qquad\qquad \downarrow \\ & \xrightarrow{k_P} [{}^3H_n]\text{dihydrothymine} \end{array} \quad (8)$$

If the reaction proceeds with 100% tritium, $n = 2$ for the hydrogenation product of thymine, and $n = 3$ for the hydrogenation product of [^{3}H]thymine. Since the experiments were performed not with tritium but with a hydrogen–tritium (1000 : 1) mixture, the number of product molecules containing several tritium atoms is negligibly small, i.e., $n = 1$. This scheme is stoichiometrically different from scheme (4), but each reaction in scheme (8) seems to occur in two steps: the isotopic exchange reaction including the break-off of the H atom from thymine, so that the $^1H^3H$ molecule is formed, and recombination of the resultant radical with the other $^3H_{sp}$ atom; the hydrogenation reaction includes the attachment of $^3H_{sp}$ at the double

TABLE 1

Results of Regression of Data on the Kinetics of Total Radioactivity Accumulation by Eqs. (1), (2), and (3)

Reaction temperature	Eq. no.	a (min^{-1})	b (Ci/mole)	r.s.d.r.[a]	r.s.d.m[b]
70°C	(1)	1.44	19.1	26.9%	
	(2)	0.144	104	38.2%	
	(3)	0.131	102	40.6%	
45°C	(1)	0.791	5.72	21.5%	
	(2)	0.107	27.8	33.5%	
	(3)	0.0982	27.1	40.0%	
20°C	(1)	0.379	3.40	25.6%	
	(2)	0.0492	19.2	41.2%	25%
	(3)	0.0469	18.8	44.3%	
0°C	(1)	0.217	2.45	25.6%	
	(2)	0.0376	11.3	35.8%	
	(3)	0.0357	11.0	33.8%	
−25°C	(1)	0.0649	1.24	24.9%	
	(2)	0.0166	4.24	30.1%	
	(3)	0.0160	4.05	34.3%	

[a] r.s.d.r.—relative standard deviation for regression.

[b] r.s.d.m.—relative standard deviation of measurements (the coefficient of variation).

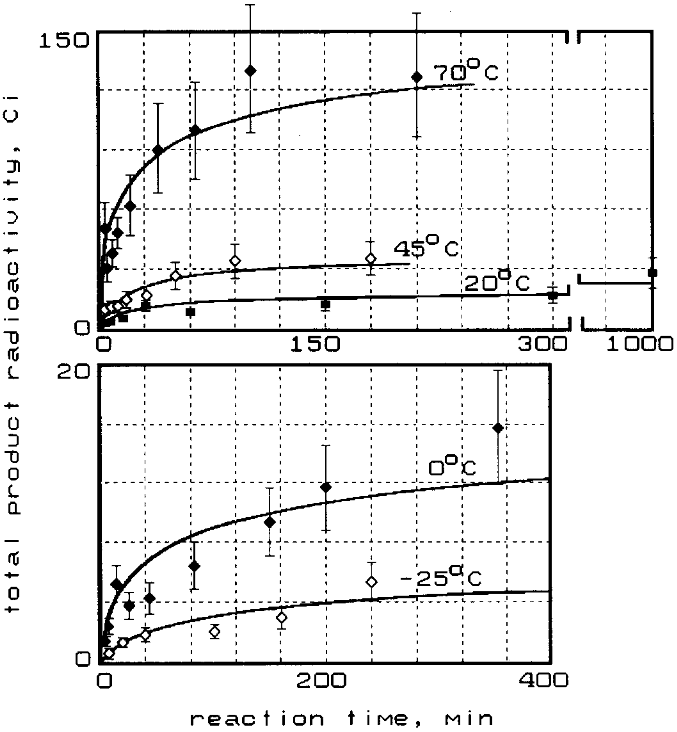


FIG. 3. The kinetics of total product radioactivity accumulation (thymine radioactivity + dihydrothymine radioactivity per 1 mole of initial thymine).

bond and the recombination of this radical with the other $^3H_{sp}$ (*14*). The reactions of radical recombinations proceed almost without activation energy and their rate constants are several orders of magnitude higher than those of the first steps; i.e., it is the first steps that determine the rate in both reactions. That is why the reaction of thymine tritiation (8) examined in this paper is kinetically consistent with the scheme (4), and Eqs. (5–7) apply to this case.

Figure 3 shows the kinetics of total radioactivity accumulation in the reaction products (the radioactivity of thymine + the radioactivity of dihydrothymine) for the following temperatures: −25, 0, 20, 45, 70°C.

Table 1 presents the results of the regression (minimizing the sum of the squares of the differences between the theoretical function and the experimental values weighed by reverse variances) of these data by kinetic equations (1), (2), (3). Since Table 1 is about the kinetics of total radioactivity accumulation, the parameter a for the diffusion model is the parameter $a_P + a_{RT}$ of Eq. (7). The table shows that r.s.d.r. (the relative standard deviation for regression) by the diffusion model equation is less than or roughly equal to r.s.d.m. (the relative standard deviation of measurements = the coefficient of variation). Moreover, the r.s.d.r. by equations of the catalyst poisoning models is considerably larger than the r.s.d.m. or the r.s.d.r. by the diffusion model equation. Table 1 suggests that out of the three available equations only the diffusion model equation adequately describes the experimental data on the kinetics of total product radioactivity accumulation.

Figure 4 shows the kinetics of the changing ratio of thymine and dihydrothymine ra-

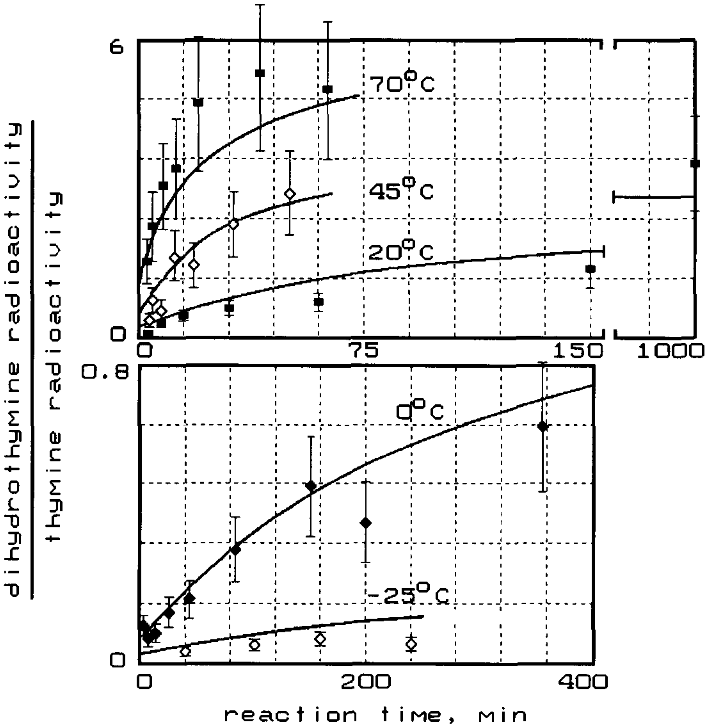


FIG. 4. The kinetics of thymine to dihydrothymine radioactivity ratio.

dioactivities. Since the experiments were performed with hydrogen–tritium (1000 : 1) mixture, the number of product molecules containing several tritium atoms is negligibly small. Therefore the radioactivity ratio of the products is in this case equal to the ratio of their amounts. One can see from the experimental data in Fig. 4 that:

(i) the ratio of the forming amounts of dihydrothymine and [^{3}H]thymine grows many times while the reaction rate rapidly decreases, the growth rate being the highest at the beginning of the reaction. Hence *the reaction kinetics is determined by the concentration gradient of spillover hydrogen in the organic phase.*

It follows from Eq. (5) and (6) that the ratio of product amounts at the beginning of the reaction ($t \rightarrow 0$) is equal to the ratio of the rate constants k_P/k_{RT}. Figure 5c shows the temperature dependence of the rate constant ratio. The ratios were obtained through a straight-line approximation of initial (approximately linear) sections of the dependences in Fig. 4. The temperature dependence of the rate constant ratio can be expressed by the following empirical formula:

$$k_P/k_{RT} = 10^{3.8\pm0.4}\exp[-(6100 \pm 600\,[\text{cal/mol}])/RT]. \quad (9)$$

It follows from the formula that upon temperature reduction the reaction rate of dihydrothymine formation drops considerably quicker than the rate of isotopic exchange; i.e., by lowering temperature one can "suppress" a side reaction (if the target product is isotope-substituted compound): at $t^\circ = -42.5°\text{C}$, $k_P/k_{RT} = 0.01$. This observation can be accounted for if we proceed from the hypothesis that the crystal environment can hamper the formation of some hydrogenation products.

If we know the ratios k_P/k_{RT} and the parameters a_{RT} we can build the theoretical time dependences of the product amounts

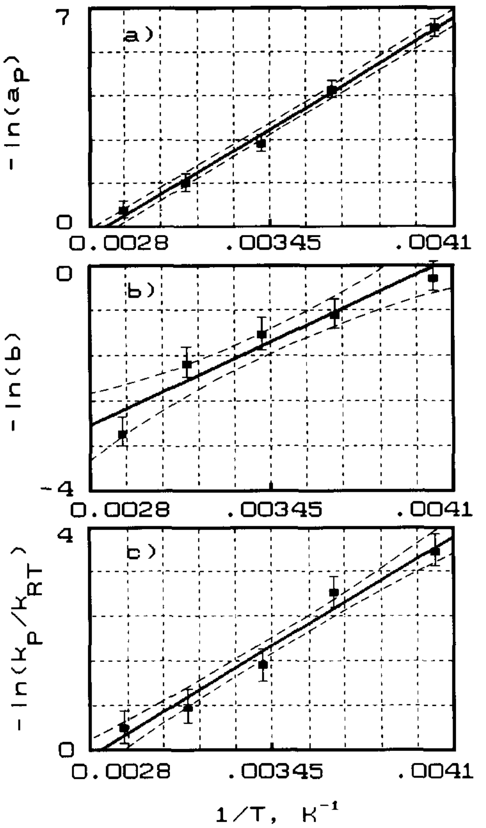


FIG. 5. Temperature dependences: (a) of the a_P parameter, (b) of the b parameter, (c) of the rate constant ratio k_P/k_{RT}. Standard errors of function prediction are shown by the dashed line.

forming in the reaction. Such dependences are shown in Fig. 4. The conclusion one can draw from the figure is that *there is a satisfactory quantitative agreement between the diffusion model and the experimental data on the kinetics of the product amount ratio.*

As follows from the explanation to Eqs. (5)–(7), the parameters a_P and b are products of multipliers raised to different powers, each of which can be represented in the Arrhenius's form. Therefore the parameters a_P and b can be represented in the Arrhenius's form. In this case the energy of activation will be a certain effective value. The temperature dependence of the parameters a_P and b are shown in Fig. 5a and 5b. The parameters a_P are calculated from the known $a_P + a_{RT}$ and k_P/k_{RT} by the formula

$$a_P = (a_P + a_{RT})/(1 + (k_P/k_{RT})^{-1}).$$

The regression analysis of these data produces the empirical formulas,

$$a_P = 10^{6.6\pm0.4}\exp[-10600 \pm 500\,[\text{cal/mol}])/RT], \quad \text{sec}^{-1} \qquad (10)$$

$$b = 10^{4.0\pm0.6}\exp[-(4500 \pm 700\,[\text{cal/mol}])/RT], \quad \text{Ci/mol} \qquad (11)$$

The standard errors of the parameters given in the empiric equations (9)–(11) are errors of their determinations by use of the regression, which in this particular case is made in a way traditional for chemistry: this is the linear function regression in coordinates −ln(function) vs $1/T$. It should be stated that the known rule of the function error calculation by the errors of independent variables cannot be applied to the calculation of function prediction errors proceeding from errors of parameters, for the latter ones are not independent. Standard errors of function prediction by formulae (9)–(11) are shown by the dashed line in the corresponding graphs (Fig. 5a–5c).

From the practical standpoint, the obtained empiric formulae are interesting because they allow calculation of the reaction temperature and time for preset characteristics of the final products, the molar radioactivity of the tritium substituted thymine, and the content of dihydrothymine in reaction products.

Further studies of the SSCH mechanism must include the elucidation of both crystal packing and chemical structure effects on the reaction process. With this aim in view, it is necessary to compare reactions carried out with different compounds and in reaction mixtures prepared in different ways. This first stage of a similar study could probably be performed on a comparison basis by empiric formulae similar to those obtained here, because each of the numeric parameters of the formulae characterizes a comparatively narrow range of processes in the reaction system.

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