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Thermal Stability of an Oligosaccharide: Autocatalytic Behavior

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Abstract:

Many of the materials in the pharmaceutical industry can present hazards, and it is essential to have a good knowledge of the thermal stability of every material to be able to assess any risk. Not only raw material and final products must be studied but also reaction intermediates. In this way, a safety study of a Sanofi-Synthelabo process pointed out the thermal instability of an isolated intermediate from an oligosaccharide pharmaceutical active ingredient synthesis. This led to a detailed kinetic study to give suitable safety recommendations to industrials for handling and storage of this product. The differential scanning calorimetry (DSC) was the technique used to perform the study. Dynamic and isothermal analyses underlined the autocatalytic behavior of the product. Activation energy, time to maximum rate (TMR), and critical storage radius were evaluated, and to complete the study the compatibility with materials (glass, aluminum, and stainless steel) has also been tested.

Introduction

Safety studies of chemical processes must follow a rigorous methodology where every kind of hazard is examined to give suitable safety recommendations to industrials. The first step in such a study is to assess the thermal hazard of reactants (by DSC, adiabatic techniques, etc.). The next step is to determine the thermodynamic and kinetic properties of the reaction (reaction calorimetry). The stability of different reaction mixtures must not be forgotten because they may also present a thermal hazard. We strongly recommend theuse of adiabatic techniques for these mixtures to reproduce if possible industrial conditions (good range of temperature, stirring, representative sample, etc.) and to get pressure information. Afterwards the thermal stability of the products is also studied. If any risk of thermal runaway is suspected, then further studies are performed to determine the thermodynamic and kinetic properties of the runaway.

In this way, the thermal instability of a pure intermediate was pointed out by a safety study of a Sanofi-Synthelabo process.

It was found that this intermediate, an oligosaccharide, decomposed violently. Therefore, a further study was performed to assess as much as possible the hazards of the product and to give the best recommendations to industrials for handling and storage.

The differential scanning calorimetry (DSC) is one of the techniques used to perform this study. Indeed, DSC is an excellent and one of the most common techniques for early determination of thermal hazards in a reaction study. It needs only few milligrams of product and gives results rapidly. Whereas this study was completed with adiabatic tests, this report only deals with DSC experiments.

Dynamic and isothermal analyses underlined the autocatalytic behavior. Kinetic parameters, activation energy, time to maximum rate, and critical storage radius were also evaluated.

The compatibility of the product with materials (glass, stainless steel, aluminum) was also analyzed to complete the study.

Experimental Section

Experiments were performed on two DSC apparatus from Mettler Toledo: DSC 821e and DSC HP27e.

The DSC 821e allows working with aluminum cells (40 μL, up to 0.2 MPa overall pressure-resistant) and stainless steel (120 μL, up to 2 MPa overall pressure-resistant).

The second system, DSC HP27e, allows working with glass cells. It is possible to work in an open cell under pressure.

STARe software was used to acquire and evaluate data.

The principle of measurement is the one of Boersman or heat flux measurement: temperatures and heat flux linked with the material thermal transitions are measured as a function of temperature or time.

Theoretical Calculations

Thermodynamic and kinetic parameters of the decomposition can be determined by dynamic and isothermal measurements.

Dynamic Measurement. *Activation Energy Determination by Kissinger Method.*[1] The reaction of decomposition follows an Arrhenius law and is related to the extent of reaction a, and the rate of reaction can be written as

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[1] Kissinger H. E. *Anal. Chem.* **1957**, *29*, 1702−1706.

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$$\frac{d\alpha}{dt} = f(\alpha)A\exp\left(-\frac{E_a}{RT}\right) \tag{1}$$

If we assume that the maximum rate of reaction corresponds to the temperature of the maximum of the exothermic peak (T_p), then in that case:

$$\left(\frac{d^2\alpha}{dt^2}\right)_{\alpha_p} = 0 \tag{2}$$

where α_p is the extent of reaction corresponding to the temperature T_p.

Therefore

$$f'(\alpha_p)\frac{d\alpha}{dt} = -f(\alpha_p)\frac{E_a}{RT_p^{\,2}}\cdot\frac{dT}{dt} \tag{3}$$

With $\gamma = (dT/dt)$ rate of temperature programmed and substituting the expression 1 for ($d\alpha/dt$), then:

$$\ln\left(\frac{\gamma}{T_p^{\,2}}\right) = \ln\left(-\frac{RA}{E_a}\cdot f'(\alpha_p)\right) - \frac{E_a}{R}\cdot\frac{1}{T_p} \tag{4}$$

Activation energy E_a is the slope of the straight line $\ln((\gamma/T_p^{\,2})) = f((1/RT_p))$.

This method does not assume any kinetic mechanism.

Isothermal Measurement. It is possible to determine the isothermal induction time and the maximum thermal flux by isothermal DSC at different temperatures. These values are used to determine different parameters necessary for safety recommendations, such as activation energy, time to maximum rate, and critical storage radius.

Depending on the assumption made on the mechanism of the decomposition reaction, the results may be different.

To be the most conservative from the point of view of safety, calculations under different assumptions (*n*-order or autocatalytic kinetics) are performed, and the safest results are retained.

Activation Energy Determination. If the decomposition is assumed to follow an *n*-order kinetics, then the general expression of heat production versus temperature can be expressed by the Arrhenius law:[2]

$$Q = A\exp\left(-\frac{E_a}{RT}\right) \tag{5}$$

Thus, at the maximum of the exothermic peak:

$$\ln(Q_o) = \ln(A) - \frac{E_a}{RT_o} \tag{6}$$

Then by plotting $\ln(Q_o)$ against $-(1/RT_o)$ it is possible to determine the activation energy.

For the autocatalytic decomposition it is different. The autocatalytic behavior can be underlined by plotting the maximum heat production Q_o and the induction time τ in logarithmic scale against temperature in reciprocal scale: if the reaction is formally autocatalytic, then the plots are lines with respective slopes of E_a/R and $-E_a/R$.[3]

Time to Maximum Rate determination. The time to maximum rate (TMR) is the time after which, from a given initial temperature, a product reaches its maximum rate of decomposition in strictly adiabatic conditions.

This is for a given temperature, the induction time that is observed to reach the maximum of decomposition.

The TMR can be expressed by the following equation:[2]

$$\text{TMR} = \frac{C_pRT_o^{\,2}}{Q_oE_a} \tag{7}$$

This equation is valid for zero-order reaction.

Nevertheless, this equation can be applied for *n*-order kinetics if the ΔT_{ad} is quite high[2] because in this case the Arrhenius part of the reaction rate eq 1 is predominant. The influence of the degree of conversion is neglected.

However, some precautions must be taken with autocatalytic reaction. Grewer[4] gives an equation to calculate the TMR for formal autocatalytic reactions:

$$\text{TMR} = k_o^{\,-1}\exp(\beta B)E_a\beta B \tag{8}$$

with:

$$\beta = \exp(-kt_{max}) \tag{9}$$

$$B = \frac{E_a\Delta T_{ad}}{RT_o^{\,2}} \tag{10}$$

$$k = \frac{\ln(3 + \sqrt{8})}{t_{max} - t_{1/2}} \tag{11}$$

k_o is the rate constant at the temperature T_o.

Experimentally the factor β represents the degree of autocatalysis: the smaller is β, the more autocatalytic is the reaction.

Critical Storage Radius Determination. This determination is based upon the F. Kamenetskii theory.[2,4,5]

This model forecasts that the heat dissipation is made by conduction in solid medium. Nothing is opposed to the heat transfer at wall face barrel level: the product temperature near the wall is the same as the room temperature. The user must keep in mind that it is not the case with some containers.

The critical radius storage is the radius of storage packaging beyond which there is thermal runaway. It depends on the size and shape of the system and also on the external temperature.

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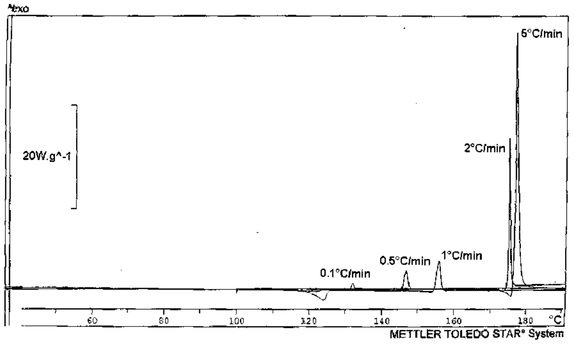
(2) Barton, J; Rogers, R. *Chemical Reaction Hazards,* 2nd ed.; Institution of Chemical Engineers: Rugby, UK, 1997.

(3) Riethmann, J.; Stoessel, F. Sécurité thermique des procédés chimiques, données, critères de jugement, mesures, traduction (Thermal Safety for Chemical Processes, Data, Decision Tool, Measurements, Data Reduction, Engl. Transl.). *Cahiers de Notes de Documentaires* **1991**, *144, 145,* ND1837.

(4) Grewer, T. *Thermal Hazards of Chemical Reactions*; Elsevier: Amsterdam, 1994; pp 23−27.

(5) Frank-Kamanetskii, D. A. *Diffusion and Heat Transfert in Chemical Kinetics*, 2nd ed.; Plenum Press: New York, London, 1969.

Chart 1. **Dynamic DSC studies**



The basic equation is:

$$r = T_a \sqrt{\frac{\lambda RS}{(-\Delta H_R)E_a\rho A \exp\left(-\frac{E_a}{RT_a}\right)}} \tag{12}$$

S is a dimensionless critical parameter that depends on the shape, size, and boundary conditions of the material. For a cylinder the value of *S* is 2.

The thermal conductivity λ is determined by the Weber equation:

$$\lambda = 3.59 \times 10^{-3} C_p \frac{\rho^{4/3}}{M^{1/3}} \tag{13}$$

Results and Discussion

Initial studies consisted in ramped DSC screening tests on a laboratory batch. The tests performed at the heating rate of 2 °C min^{-1} showed that the product could decompose exothermically with a heat of decomposition of around 460 $\text{kJ}\cdot\text{kg}^{-1}$.

The decomposition temperature (temperature where the DSC signal stands out the baseline) in these tests was around 170 °C (Chart 1).

As the product was assigned to be dried and to be stored, further studies were performedto determine the characteristics of the decomposition and the recommendations to give to industrials for handling this intermediate.

First of all, dynamic tests were performed to determine the activation energy of the decomposition.

After that isothermal measurements were performed to assess any risk and to evaluate any thermokinetic parameters.

Dynamic Study. Further dynamic studies at various heating rates on the laboratory batch led to the determination of the activation energy by the Kissinger method which was found to be 94.8 ± 12.8 $\text{kJ}\cdot\text{mol}^{-1}$ (Charts 1 and 2). It can be seen on Chart 1 that the exothermal detection temperature depends a lot on the sample heating conditions. Autocatalytic effects induce a difference of 40 °C between experiments at 2 and 0.1 °C/min.

Isothermal Study. To determine the time to maximum rate, isothermal DSC experiments were performed at different temperatures (Chart 3).

It can be seen on these graphs that the decomposition occurs after a certain induction time and that this time decreases when the temperature increases.

Chart 2. **Activation energy determination by Kissinger method**

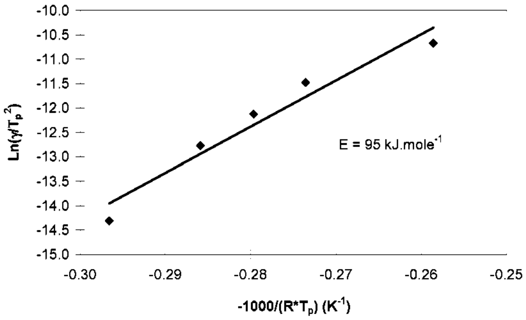
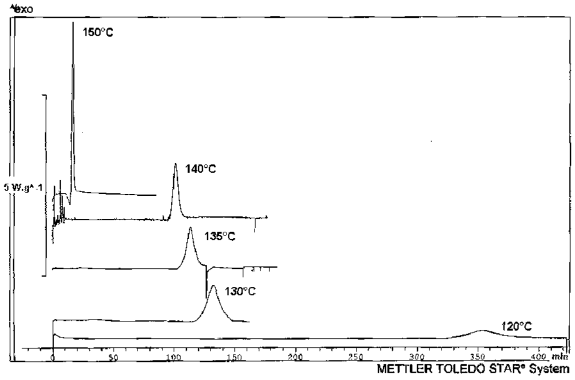


Chart 3. **Isothermal DSC studies**



This phenomenon is typical of a complex autocatalytic decomposition. The author wants to draw your attention to chemicals containing leaving groups such as mesylate and tosylate which can induce this kind of effect.

Then the calculations were made with different models (assumption of a kinetics of *n*-order or formally autocatalytic) to determine the safest drying and storage conditions.

Under *n*-order kinetics assumption of eq 6 is used to determine Arrhenius parameters and eq 7 for the TMR.

Under the assumption of an autocatalytic decomposition the calculations are more complex:

k is first calculated with eq 11. Then β is deduced from these values by eq 9. The geometric mean of β values is calculated and used to calculate *k* values with eq 9.

As *k* is the rate constant, these mean values of *k* are used to evaluate the Arrhenius parameters E_a and ln(*A*) according to the Arrhenius equation:

$$k = A \exp\left(-\frac{E_a}{RT}\right) \tag{14}$$

These values of E_a and *A* are used to determine the autocatalytic TMR according to eq 8.

The adiabatic temperature increase ΔT_{ad} is determined from mean values of isothermal decomposition energies and an estimated specific heat of 2000 $\text{J}\cdot\text{kg}^{-1}\cdot\text{K}^{-1}$.

Results are presented in Tables 1 and 2.

The difference between these values and the value obtained by the Kissinger method can be explained by the different assumptions made about the reaction mechanism (with the Kissinger method, no assumption was made).

The difference of activation energy found between the calculation from ln Q_o and ln τ shows that the mechanism

Table 1. **Arrhenius parameters determination**

kinetics	E_a (kJ·mol^{-1})	ln A (s^{-1})	β	ΔT_{ad} (°C)
n-order ln $Q_o = f(1/RT)$ (Chart 4)	135.1 ± 15.6	40 ± 4.6	–	
autocatalytic ln $\tau = f(1/RT)$ (Chart 4)	111.1 ± 9.8	30.3 ± 2.9	–	
autocatalytic ln $k = f(1/RT)$ (Chart 5)	111.1 ± 9.8	28.0 ± 2.9	2.6×10^{-3}	272

Table 2. **Determination of time to maximum rate under assumption of *n*-order kinetics and autocatalytic kinetics**

kinetics	TMR
n-order	23 d at 25 °C 20 h at 50 °C 1 h at 75 °C
autocatalytic	23 d at 122 °C 20 h at 161 °C 1 h at 196 °C

Chart 4. **Activation energy determination by isothermal measurement (*n*-order assumption: ln Q_o versus (1/*RT*), autocatalytic assumption: τ versus (−1/*RT*))**

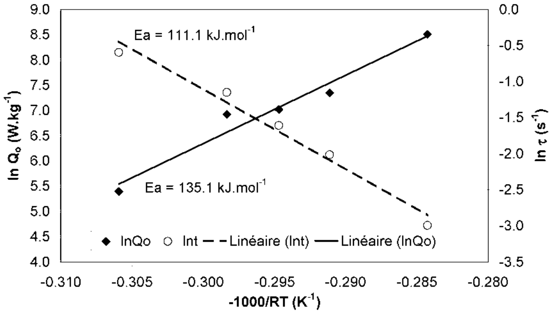
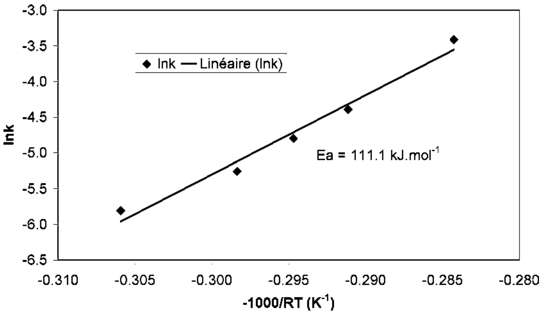


Chart 5. **Activation energy determination by isothermal measurement (formal autocatalytic assumption)**



of decomposition is not formally autocatalytic but more complex (Charts 4 and 5).

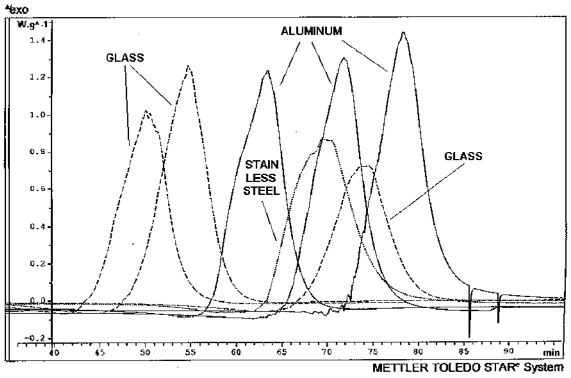
The results for TMR obtained with relation 8 are more conservative; then, for safety reasons the results obtained under autocatalytic assumption are rejected.

As this intermediate was assigned to drying and storage, the critical radius storage has been determined.

The thermal conductivity was calculated from the eq 13:

$$\lambda = 0.025 \text{ W·m}^{-1}\text{·K}^{-1}$$

Chart 6. **Material interaction study**



and the critical storage radius was evaluated for a cylinder the height of which is equal to 3 times its radius according to eq 12.

The calculations gave a critical radius of 15 cm at 40 °C and of 43 cm at a temperature of 20 °C.

The same experiments were performed on different industrial batches, and these experiments showed a low reproducibility of phenomenon. In the same way, isothermal analyses at 135 °C on different batches underlined the low reproducibility of tests.

This can be explained by eventual traces of impurities. Indeed traces of impurities may lower the thermal stability of the product to a large extent.[6] The solvent content can also have an influence on the decomposition. For these reasons, making such assessments using laboratory-derived material is not enough for industrial recommendations. However, it was noted that the critical storage radius and TMR were similar for every experiment under a zero-order assumption kinetics (safer assumption).

Material Interaction Study. The DSC analyses at 135 °C with different kinds of cell materials: glass, aluminum, and stainless steel did not show any differences (more than reproducibility). The influence of impurities of various industrial batches is more significant than sample−crucible interaction (Chart 6).

Conclusions

This product presents a highly exothermic autocatalytic decomposition. Drying, storage, and transportation of this intermediate must be done very carefully. As results from both methods are so different, this study was completed by adiabatic tests. One of these tests showed a TMR of 35 h at 80 °C. **Therefore, it is first recommended to develop a new process to avoid isolation of this product**.

During this period, the following conditions must be applied:

(1) Drying should be done at a maximum of 50 °C in a jacket with **control of temperature** during a maximum of 48 h with safety alarms if the temperature increases.

(2) Storage should be in a cardboard cylinder in amounts that do not exceed 50 kg.

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(6) Gustin, J. L. Influence of trace impurities on chemical reaction hazards. *J. Loss Prev. Process Ind.* **2002**, *15*, 37−48.

(3) The maximum duration of storage in the workshop at room temperature should not exceed 3 days maximum, and duration of storage in the warehouse should not exceed 3 months maximum at 5 °C.

(4) Caution must also be taken during transportation.

Nomenclature

Variables

A	preexponential factor
B	thermal reaction parameter
C_p	specific heat capacity [J•kg^{-1}•K^{-1}]
E_a	Arrhenius activation energy [J•mol^{-1}]
ΔH_R	enthalpy of reaction [J•mol^{-1}]
k	rate constant
k_o	rate constant at $T = T_o$
m	mass of sample [kg]
M	molar mass [kg mol^{-1}]
Q_o	heat release rate at T_o [W•kg^{-1}]
r	critical storage radius [m]
R	universal gas constant [J•mol^{-1}•K^{-1}]
S	constant
T	temperature [K]
ΔT_{ad}	adiabatique temperature increase [K]
T_a	storage temperature [K]
T_p	temperature at maximum of exothermic peak [K]
T_o	initial temperature [K]
t	time [s]
$t_{1/2}$	half-life time [s]
t_{max}	time to maximum rate (autocatalytic reaction) [s]

Greek Symbols

α	extent of reaction
β	rate coefficient of autocatalytic reaction
γ	rate of temperature programmed [K•min^{-1}]
λ	thermal conductivity [W•m^{-1}•K^{-1}]
ρ	density
τ	induction time [s]

Abbreviations

DSC	differential scanning calorimetry
TMR	time to maximum rate [s]

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