



Calculations for the prediction of long-term stability using the thermal and kinetic parameters measured by the Thermal Activity Monitor

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INTRODUCTION

In the chemical and pharmaceutical industries, there is a continuing demand for a rapid method for the determination of long-term stability. This information is required during the development of new formulations as well as in the routine quality control of established products.

Using the Thermal Activity Monitor (TAM), half lives of up to forty years can be determined within three hours. This application note describes methods for estimating the thermal and kinetic parameters of a chemical degradation or reaction process from the output of TAM.

EXPERIMENTAL

Test substances require no pretreatment and are presented directly to the instrument in sealed ampoules. Measurements are made at the normal storage temperature. Differential heat flow data in μW are collected continuously through the Digitam software program. In some cases, sufficient data can be collected within three hours to enable the calculations described below to be performed. In other cases, it may be preferable to monitor reactions over an extended period. Alternatively samples may be measured then removed from TAM and stored for periods of weeks or months before being measured again after storage.

CALCULATIONS AND DISCUSSION

At its most sensitive, TAM can discriminate between signals that differ by $0.1 \mu\text{W}$ ($0.1 \mu\text{Js}^{-1}$). Therefore, under ideal conditions, a signal which differs from the baseline by $0.1 \mu\text{W}$ can be regarded as significant. By making some simple and reasonable assumptions about the value of $\Delta_{\text{R}}\eta$, the change in reaction enthalpy, it is possible to calculate the rate of a reaction from this measurement. It is also possible to estimate a value for $\Delta_{\text{R}}\eta$ from a measured reaction rate.

To put these rather abstract numbers into a context which is both useful and easily understood, consider their implications when studying a hypothetical reaction in the microcalorimeter with a modest enthalpy change of say 40 kJ mol^{-1} , approximately the enthalpy of a strong hydrogen bond.

The detectable reaction rate would then be:

$$\begin{aligned}(0.1 \times 10^{-6} \text{ Js}^{-1}/40 \times 10^3 \text{ J mol}^{-1}) &= 2.5 \times 10^{-12} \text{ mol s}^{-1} \\ &= 1.5 \times 10^{-10} \text{ mol min}^{-1} \\ &= 2.16 \times 10^{-7} \text{ mol day}^{-1} \\ &= 7.2 \times 10^{-5} \text{ mol year}^{-1}\end{aligned}$$

This represents a quite remarkable level of sensitivity. Say, for example, a signal of $0.1 \mu\text{W}$ was observed during the study of the long-term stability of a drug compound which is prone to oxidation during storage.

Assuming that

(i) the compound of interest has a relative molar mass of 400 D,

(ii) the enthalpy of oxidation is 100 kJ/mol,

(iii) a typical sample weight of 1 g was used, then the signal would be equivalent to monitoring a reaction with a half life of almost 40 years, the time taken for 0.5 g of the drug to be oxidised. The rate observed experimentally would be detected by TAM within three hours which is the total time required to load the ampoules into the instrument, wait for thermal equilibration and measure the reaction rate.

Alternatively expressed, an oxidation rate of 1% per annum of this material is readily detected.

An example of the calculation is shown below:

For $\Delta_{\text{r}}\text{H} = 100 \text{ kJ mol}^{-1}$

Mr $= 400 \text{ D}$

Sample size $= 1 \text{ g}$

then,

$$\begin{aligned}\text{Half life} &= (0.5/400 \text{ mol}^{-1}) / (0.1 \times 10^{-6} \text{ Js}^{-1} / 100 \times 10^3 \text{ J mol}^{-1}) \\ &= 1.25 \times 10^8 \text{ s} \\ &= 39.64 \text{ years}\end{aligned}$$

CONCLUSION

Thermal Activity Monitoring offers a rapid, direct, nondestructive method of quantifying chemical degradation of substances at actual storage temperatures. The method is equally suitable for use with samples in solid, liquid or mixture forms.

REFERENCES

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