an Arrhenius equation. Hammad and Müller (1998) have found clonazepam to degrade first-order in phosphate buffers at pH 7.4 and to adhere to an Arrhenius equation.

Heat conduction *microcalorimetry* has been used as a method to evaluate stability and excipient stability by a series of researchers Angerg et al., (1988, 1990, 1993). Hansen et al. (1989), and Wilson et al. (1995) have described the general method and results interpretation. Oliyai and Lindenbaum (1991) have studied the decomposition of ampicillin in solution by means of microcalorimetry.

4. FIRST-ORDER REACTIONS WITH MORE THAN ONE END PRODUCT

The considerations above have assumed that the scheme is simply a reaction of type $A \rightarrow B$, but often there is more than one decomposition product.

4.1. Consecutive Reactions of The First Order

The 1993 ICH Guidelines state that mass balance (or material balance) is

> The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 per cent of the initial value, with due consideration of the margin of analytical precision (382–384).

It is possible that the primary decomposition product itself is not stable, and in such cases the reaction scheme is

$$A \underset{k_1}{\rightarrow} B \underset{k_2}{\rightarrow} C \tag{2.13}$$

In other words, there will be more than one decomposition product. If all the products can be identified and quantitated, then it follows that *the number of moles of A, B, and C should always add up to the initial number of moles of A.* It is noted that it is the number of moles that must add up. Addition on a weight basis would be futile if there is a substantial difference between the molecular weights of the drug and the products. The guidelines recognize that it can be difficult, at times, to ascertain mass balance, partly due to analytical precision.

More often it is "unknowns" that cause the problem. If C were not identified, for instance, and was detected as a peak in a HPLC chromatogram, then its "content" is often stated as the area under the peak, using the drug as the unit of measure. But if, for instance, a UV detector is used, and C is lacking the amount of chromophores that A possesses, then the area under the C peak may grossly underestimate the amount of C.

An example of this is chlorbenzodiazepine, which hydrolyzes to the lactam form, and then further to the benzophenone (Carstensen et al., 1971). In fact in this reaction, for some of the benzodiazepines, C can progress further with the formation of the carbostyril and the acridone derivative, and some of the steps are associated with equilibrium conditions.

The rate equations governing scheme (2.13) are

$$\frac{d[A]}{dt} = -k_1[A] \tag{2.14}$$