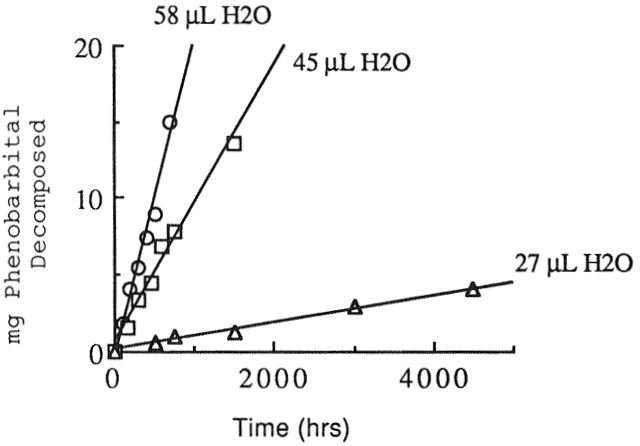

Fig. 7 Phenobarbital decomposition in the solid state at 80°C, with phosphate buffer present corresponding to a "pH" of 6.7.

are present. Carstensen and Pothisiri (1975) and Wright and Carstensen (1986) have done likewise.

In the case of very soluble drugs, e.g., ranitidine (Franchini and Carstensen, 1995; Carstensen and Franchini, 1995) the amount of moisture necessary to reach the CRH is small (i.e., the water activity (RH/100) over a saturated solution is of low magnitude). On the other hand, it is high for poorly soluble drugs.

5. KINETICALLY UNAVAILABLE (BOUND) WATER

Solid state rate constants often follow Eq. (7.2), in that they appear directly in proportion to the mass or volume of water the dosage form contains. Figure 7 presents data from the work of Gerhardt (1990) and Gerhardt and Carstensen (1989). The rate constants are pseudo zero order and are plotted versus moisture levels (Fig. 8). It is noted that the intercepts are nonzero, i.e.,

$$k_0 = k_1 S[V - w^*] \tag{7.13}$$

w^* is often called kinetically unavailable moisture or *bound water*. This is the case in many solid state reactions. The bound moisture, at times, is water of crystallization. For D,L-calcium leucovorin (Nikfar et al., 1990a,b), there are intermittent plateaus that correspond to a constant water activity (RH/100) for a series of water contents, i.e., akin to a salt pair. $[V - w^*]$ is denoted kinetically available, or more simply, *available moisture*.

Aso et al. (1997) have determined the decomposition rates of cephalotin in mixtures with pharmaceutical excipients and the effect of moisture. They found a linear relation between mobile water percentage and decomposition rate constants.

6. MICROENVIRONMENTAL pH

If a formulator is aware that a compound is more stable in an acid than in a neutral or basic environment one may often formulate it with solid acids (e.g., citric acid);