

Adsorption of Water by Anhydrous Nedocromil Sodium from 20 to 40 °C

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Abstract □ Three different powder preparations of the drug disodium 9-ethyl-4,6-dioxo-10-propyl-4*H*,6*H* pyrano[3,2-*g*]quinoline-2,8-dicarboxylic trihydrate, Nedocromil sodium (trade name Tilade), have been fully dehydrated in a vacuum and their water vapor adsorption characteristics quantitatively assessed at different water vapor pressures over a temperature range 20 to 40 °C. At saturated vapor pressures, 100% RH, rates of adsorption are around 0.1 s^{-1/2}. Graphs of square root of time against reduced mass during uptake of water vapor at vapor pressures in the range 20 to 47 mm of Hg, all equivalent to 100% RH, indicate control by a diffusion mechanism with activation energies in the range 8 to 24 kJ mol⁻¹, dependent on the powder preparation method. In two of the powders nonlinear Arrhenius-type plots are interpreted as showing that control of the process is dependent on the surface's ability to hold water molecules at the experimental temperature. The variation in activation energies and the calculated values for diffusivities, around 1 × 10⁻¹³ m² s⁻¹, are used to explore structural involvement in the overall water adsorption process. The measured values of water vapor diffusivity into the structure have been used to predict the water solubility of nedocromil sodium trihydrate, and the results show good agreement to reported solubilities. This approach to solubility prediction is an alternative to the Noyes and Whitney method where ions leaving the surface are monitored.

Introduction

Some 15 years ago a drug, C₁₉H₁₅NO₇·2Na·3H₂O, disodium 9-ethyl-4,6-dioxo-10-propyl-4*H*,6*H* pyrano[3,2-*g*]quinoline-2,8-dicarboxylic trihydrate, was found to have potential for the treatment of asthma.¹ This proved to be the most promising member of a series of salts of nedocromil acid and was simply named as nedocromil sodium (NS), now marketed as Tilade, a registered trade name. NS has been extensively characterized by chemical means². Its behavior has been compared to its acid form³ and several hydrate forms containing divalent cations.⁴ A focus of the investigations has been the relationship between water adsorption and relative humidity of finely powdered crystalline forms of the compounds together with characterization of hydrates using physical techniques. In the case of NS trihydrate a full crystallographic analysis has been achieved⁵ which shows the position of water molecules in the trihydrate form. This has led to the description of loosely bound and strongly bound water in the salt.⁵ Surprisingly, only limited information exists on rates of water uptake.⁴ Most of the experiments involved hydrates and not the anhydrous form. Reaction kinetics, from which activation energies and diffusivities can be found, do not appear to have been studied. This paper reports practical

Table 1—Forms of the Nedocromil Sodium Trihydrate Used in This Work^a

sample code	form	supplier's code no. ^b	preparation note
A	amorphous A	Bx1909R	atm at 100% RH
B	amorphous B	B-93%RH	atm at 93% RH
C	crystalline	ZBB3W	atm at 100% RH

^a All samples were of particle size 2.5 ± 0.5 μm except sample C which had a wider spread of ±0.8 μm. ^b The supplier's code number indicates the manufacturer's batch number.

work on the uptake of water vapor by anhydrous NS using thermogravimetric analysis techniques. Restrictions imposed by the fixed water vapor pressure meant that work was done at various relative humidities (RH) in a conventional Cahn balance system. This subsequently led to the development of a sensitive thermobalance housed in a controlled temperature chamber with computer-aided measuring techniques. All work with this system is done at 100% RH from which diffusivities of water in the crystal of anhydrous NS and activation energies of the controlling mechanism have been established.

Experimental Procedures

NS was supplied in various forms by Fisons Pharmaceuticals plc., Loughborough, U.K. (prior to various amalgamations), details of which and specimen codes are given in Table 1. The water was double-distilled in glass apparatus in house.

Before the experiments, each sample was dried using a standard procedure: The powders were totally dehydrated by heating to 200 °C in a vacuum to remove both the loosely and tightly bound water in the crystal structure. All samples were cooled in a vacuum of approximately 10⁻⁴ mm of Hg to room temperature before experiments were performed. The above process was carried out in situ on the balance so that samples were not exposed to air after drying.

Some samples were recycled through several dehydration—hydration—dehydration sequences in order to limit variability from physical features, such as particle size and surface area, and so produce more consistent comparative data. Constant mass changes were a control mechanism to show that the sample was cycling between anhydrous and trihydrate forms. Any variation in this pattern caused the sample to be rejected. As a further control, experiments were performed on repeat samples from the same batch. No differences could be detected in the results whether the NS was recycled several times or fresh samples were used for each temperature point.

Exploratory work was performed using an all-glass system connected to a Cahn microbalance^{6,7} with water vapor being delivered via a liquid water reservoir kept at 21 °C, i.e., a water vapor pressure of 18.65 mm of Hg. This constraint meant that RH's were in the range 100 to 39.6% RH. Experiments were timed from opening the water reservoir tap and lasted approximately 4 h. This experimental arrangement produced a fixed water vapor pressure within the system. The sample was heated by a resistance element around the sample holder capable of controlling the temperature to ±1 °C. Results were of limited value due to the range of RH. This led to the development of a new system based on a modified Cahn balance manufactured by Combustion Instrument (CI) which allowed the water reservoir to be thermostatically

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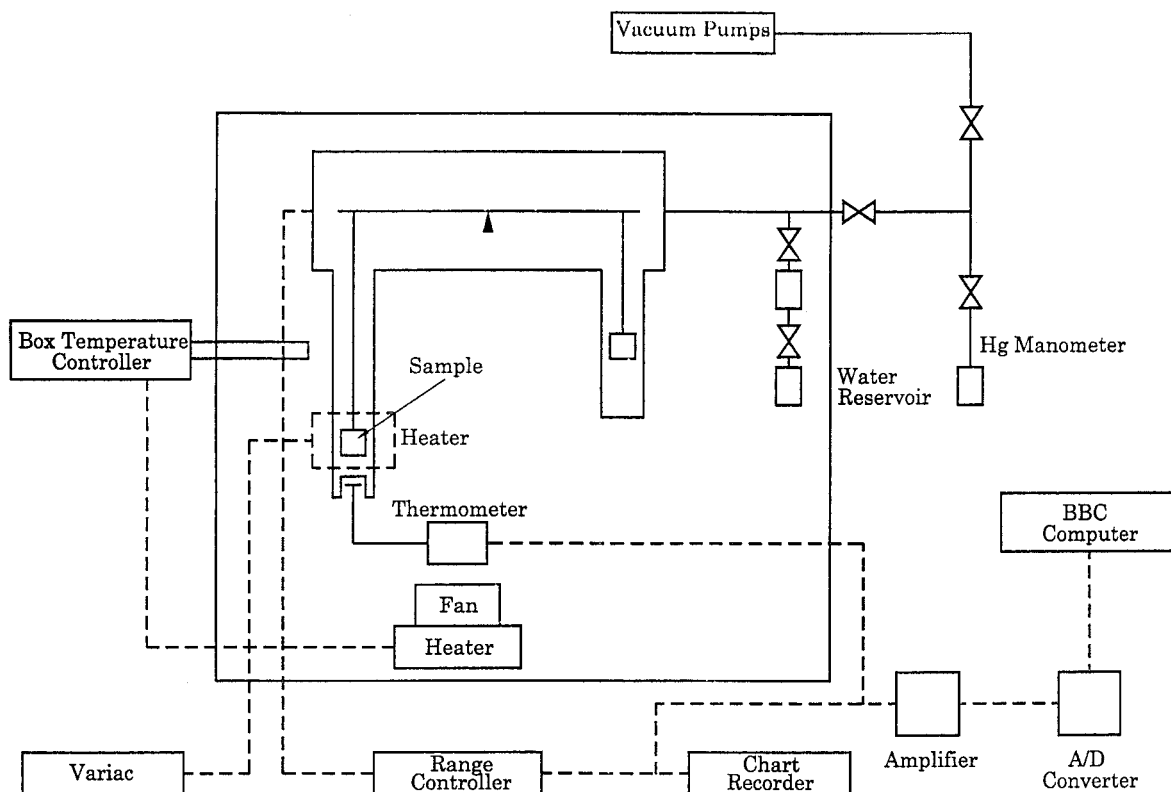


Figure 1—Schematic diagram of Combustion Instrument balance assembly.

controlled along with all itinerant connections. Control of the sample temperature was improved to ± 0.1 °C from just above room temperature up to 50 °C. A block diagram is shown in Figure 1. The mass and temperature of the specimens were measured and recorded every 5 s and could be reproduced graphically or the data processed numerically as required.⁸ Both balances are sensitive to changes in mass of 1 μ g.

Powder X-ray diffraction films were taken from the powders as supplied which confirmed differences in the degree of crystallinity. A sensitive focusing Hagg–Guinier camera was used, capable of high resolution; this showed that samples classed as amorphous were not totally amorphous because some broad, very weak Bragg lines were present.

Results

(a) Reaction at Fixed Water Vapor Pressure, Cahn Balance—The first trial experiments were conducted at a constant water vapor pressure of 18.65 mm of Hg, corresponding to a temperature of 21 °C, on the crystalline sample C, over the temperature range 22 to 40 °C. The crystallinity was qualitatively confirmed by the sharp appearance of the X-ray diffraction lines. The results were obtained graphically as time in minutes against changes in mass in micrograms. The data were represented as square root of time, t , in minutes, against $\Delta W/W_{\infty}$, the increase in mass at time t divided by the total mass gain. The decision to use the square root function came from the view that the rate most likely would be determined by a diffusion process. Several possible control mechanisms are described and investigated in a theoretical paper in preparation.⁹ Changing control processes are indicated as the graphs change from a sigmoidal curve, to linear, to two linear parts and back to sigmoidal curves as the sample temperature was increased. None of the graphs are included because a clearer view of changing control mechanisms is given in Figure 2, where the sample temperature is plotted against total mass gained after 4 h exposed to the constant water vapor pressure. These results are for

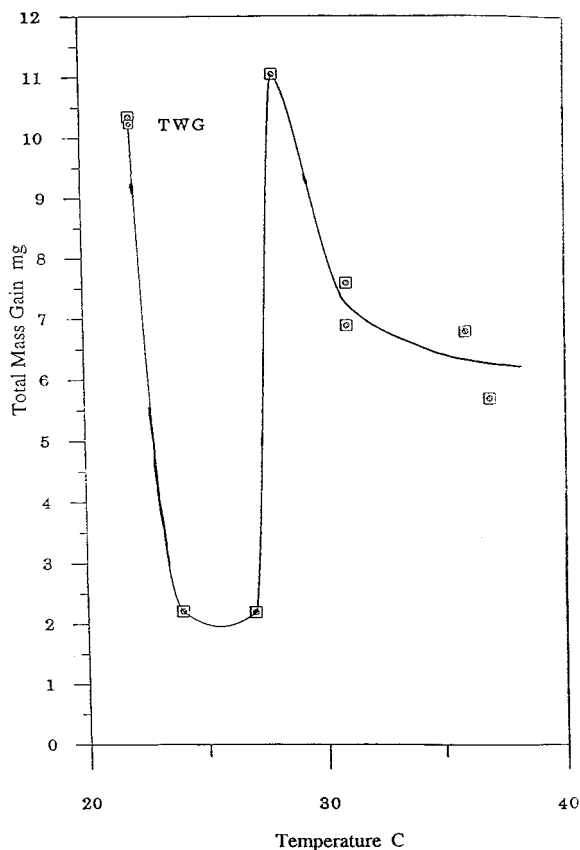


Figure 2—Plot of temperature against total mass gained after 4 h for sample C on the Cahn balance.

the same sample dehydrated by heating to 200 °C under vacuum between each water adsorption experiment. Experiments of this type are useful in delineating temperature intervals where different physicochemical processes

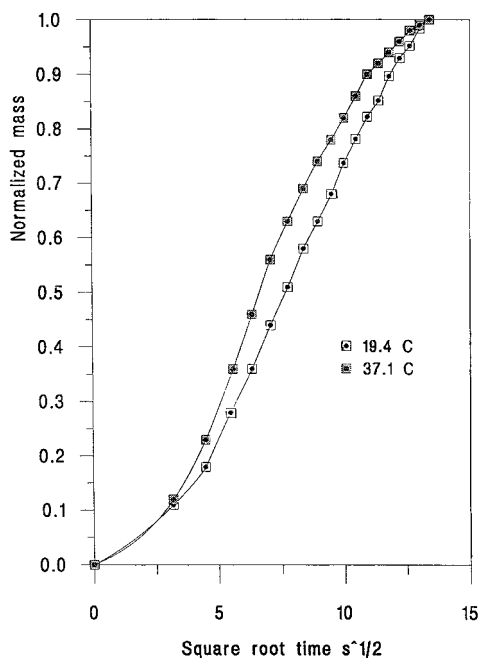


Figure 3—Examples of adsorption curves for sample A on Combustion Instrument balance.

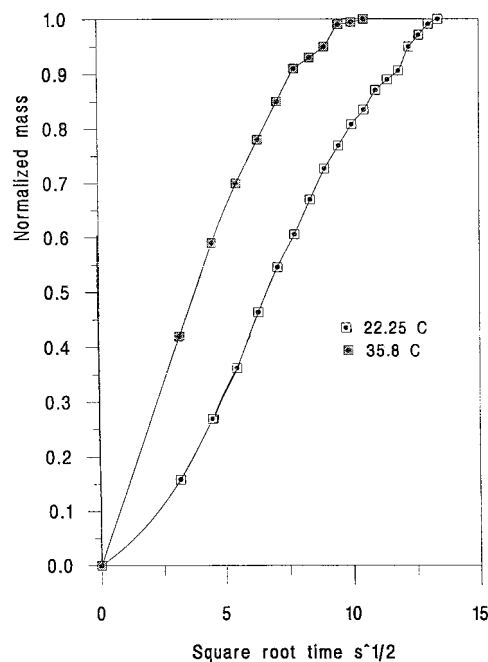


Figure 5—Example of adsorption curves for sample C on Combustion Instrument balance.

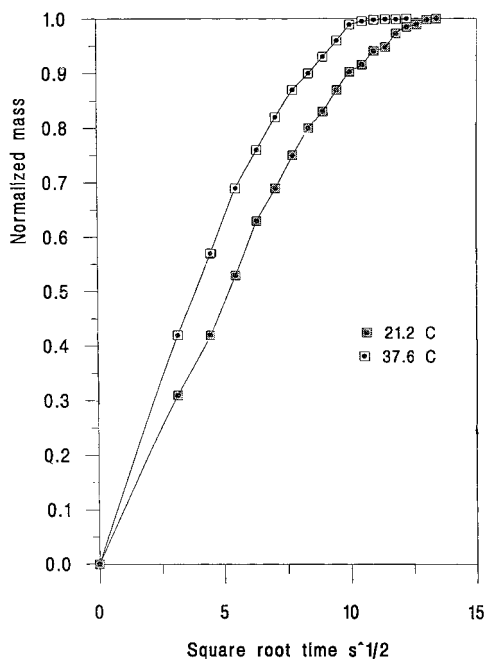


Figure 4—Examples of adsorption curves for sample B on Combustion Instrument balance.

are important and hence where more detailed experiments can be made. It is particularly useful when combined with a theoretical analysis of a model system. More detailed investigations were made at 100% RH for each temperature on the system with improved control and sensitivity.

(b) Experiments at Controlled Water Vapor Pressures, Isothermal Environment—The three samples of NS, A, B, and C, were used in the new thermogravimetric apparatus. Some of the adsorption curves are shown in Figures 3–5, which are plots of square root of time against normalized mass. All the plots are sigmoidal to a greater or lesser degree, and to proceed the rate was determined as the slope of the best fit to a straight line which fitted the experimental points between 0.2 and 0.8 normalized mass. It can be seen that considerable similarities exist

between the various forms of the drug. Table 2 contains data for sample C using both balance techniques from which some points can be drawn:

(i) When 100% RH is maintained as the sample temperature is increased (CI system), the time to achieve 60% of the total adsorption decreases with increasing temperature, i.e., the reaction rate increases with temperature throughout the temperature interval studied. These results allow activation energies to be determined.

(ii) When the water vapor was allowed to enter the sample chamber, the balance underwent a brief settling period. Following this period, in the CI system, the square root time function then produced linear adsorption curves up to at least 80% of the total adsorbed mass for all temperatures studied. This supports the view that a diffusion mechanism controls the process in these conditions. The results from the Cahn balance produce a variety of different shaped water uptake curves for a square root time function with only an intermediate temperature range being linear.

(iii) The CI balance results show that when the water vapor pressure was at saturation value the reaction rates were from 4 to 16 times faster than the Cahn balance results obtained with the restricted water vapor pressure. This was true for all the temperatures studied.

Repeat experiments involving all three forms of the drug produced similar curves to those for sample C. Forms A and B showed decreasing rates with increasing temperature over a small range, 26–31 °C. For all the results a reaction rate constant was calculated from the slope of the linear part of the square root time versus the normalized mass plots. This produced much data concerning reaction rate at specific temperatures. A plot of the reciprocal of the absolute temperature against the natural logarithm of the rates was made to extract activation energies. Figures 6–8 are examples of these plots and strongly suggest that even at 100% RH there is a temperature at which a controlling mechanism change occurs for samples A and B. The error bars shown on data points were calculated from the square root time, reduced mass curves by the binomial error expansion technique. Even with the wide uncertainty this produces, it can be seen that two lines

Table 2—Cahn and CI Balance Results for Time to 60% Uptake of Water Vapor for Drug C

Cahn balance ^a			CI system			
temp, °C (% RH)	time, min	shape of curve	temp, °C (% RH)	vapor press. water, mm of Hg	time, min	shape of curve
22 (94.1)	225	linear after 4 min	22.2 (100)	20.2	60	linear after 4 min
24 (83.3)	169	curve	23 (100)	21.1	45	linear
27 (69.7)	240	curve	26.7 (100)	26.3	45	linear after 6.25
28 (65.6)	361	linear after 9 min.	28.2 (100)	28.7	36	linear after 9 min
31 (55.3)	169	linear	31.6 (100)	34.9	35	linear
36 (41.9)	272	curve	35.8 (100)	44.1	20	linear
37 (39.6)	196	curve	37 (100)	47.1	20	linear

^a Constant water vapor pressure of 18.7 mm of Hg.

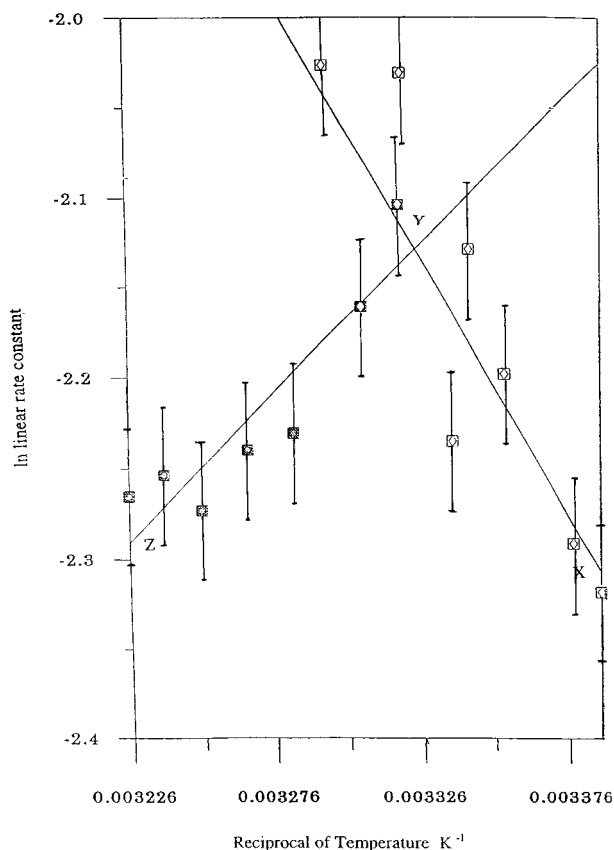


Figure 6—Arrhenius plots of the reciprocal of temperature against natural logarithm of linear rate constant for sample A.

must be drawn through the Arrhenius data, in the cases of samples A and B, while form C gives an almost normal Arrhenius plot throughout the temperature range. This seems to imply a feature of the reaction which involves the physical form of the sample.

From Figure 8, an Arrhenius plot for the crystalline sample C, the line XY corresponds to an activation energy of 8.2 kJ mol⁻¹. The two samples, A and B, show increased activation energies from lines XY in Figures 6 and 7, of 23.6 and 18.7 kJ mol⁻¹, up to temperatures of 26 and 31 °C, respectively. After these temperatures, a negative activation energy is indicated by the lines YZ in Figures 6 and 7. Hence, an interesting feature of the results is the way the form of the drug appears to influence both the activation energy and the temperature at which there is an apparent negative activation energy, see Table 3.

Discussion

The data reported here are supported by earlier indications in the literature as to the rates of water vapor uptake

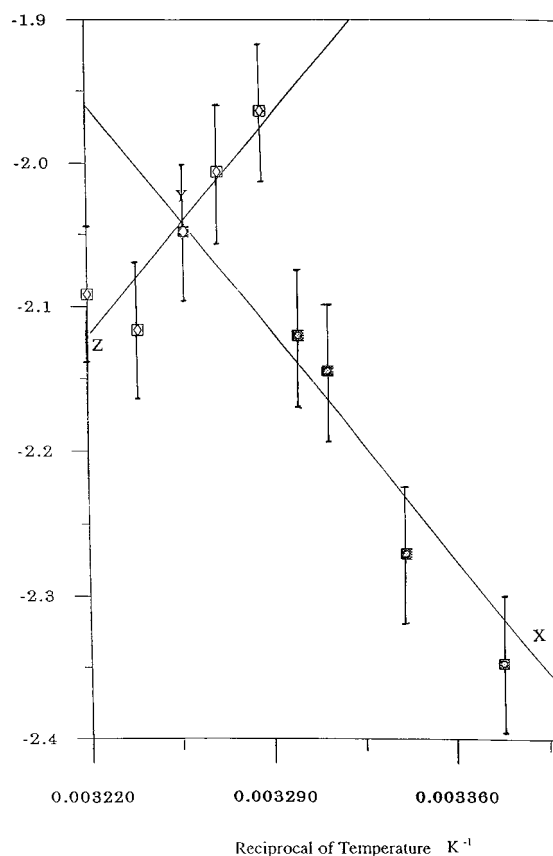


Figure 7—Arrhenius plots of the reciprocal of temperature against natural logarithm of linear rate constant for sample B.

of the anhydrous acid form of nedocromil.³ Our results for NS show that a second or more elapses before any adsorption is recorded on a sensitive system, and then adsorption rates are modest, around 0.1 s^{-1/2}. The literature shows that nedocromil magnesium hydrates also do not appear to absorb water rapidly because Zhu et al.⁴ noted that several months in environments saturated with water vapor are needed to increase the crystal water content of the salt to saturation values. In both the acid and magnesium forms of nedocromil, dissolution of the solid into liquid water was reported as a slow process, and this was rationalized using forms of the Noyes–Whitney equation¹⁰ of dissolution kinetics.

Khankari et al.² have reported gravimetric experiments performed on anhydrous NS in different relative humidities. The importance of the RH parameter was demonstrated but no indication of the actual time taken to adsorb water at critical relative humidities was given; hence, no conclusions about rates of adsorption can be made from that work.

Why and where the critical temperature for reaction rate changes at 100% RH, seen in this research, occurs need

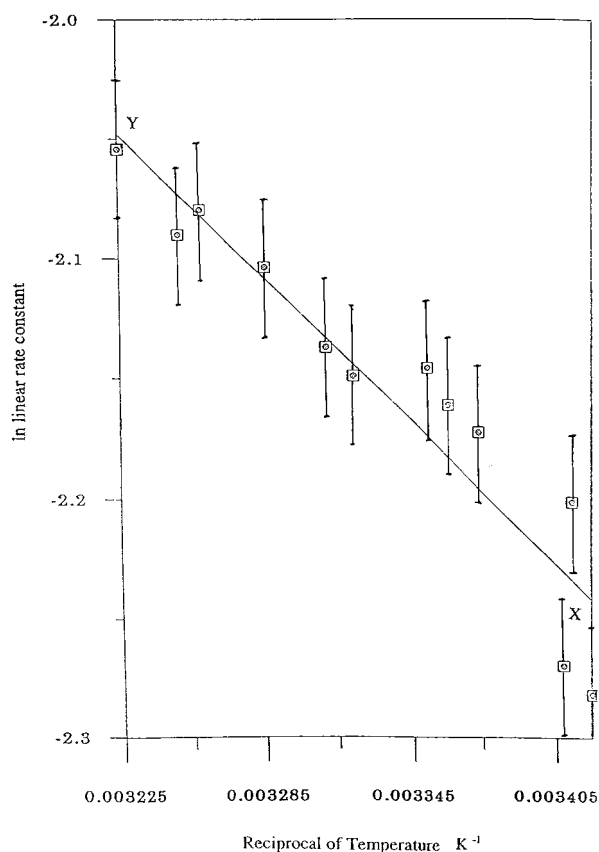


Figure 8—Arrhenius plots of the reciprocal of temperature against natural logarithm of linear rate constant for sample C.

Table 3—Activation Energies Calculated from Thermogravimetric Balance Results^a

form of drug	balance	temp of process change, °C	activation energy (XY) kJ/mol	activation energy (YZ) kJ/mol
C (crystalline)	Cahn	26	—	-88.4
A (amorphous)	Cl	26	23.6	-17.1
B (amorphous)	Cl	31	18.7	-18.3
C (crystalline)	Cl	—	8.2	—

^a X, Y, and Z refer to the lines in Figures 6–8.

more detailed investigation using a wider range of techniques. This question is presently being probed using desorption studies from fully hydrated samples as a means to a better understanding of the mechanisms of hydration.

When the humidity is controlled so that vapor phase diffusion is not rate-limiting, diffusion of water in the solid can be the controlling feature, and the mostly linear graphs of square root time against normalized mass suggest that this situation applies here. The rate constants derived from the linear slopes for experiments done at 100% RH allow activation energies to be obtained. The values found here for activation energies, for the adsorption process when availability of water molecules is not limiting, show that the lowest energy barrier is associated with the crystalline form of NS, see Table 3. The answer to questions regarding the activation energy changes might at first seem to be associated with total surface area i.e., the amorphous forms of the drug having a greater surface area, and surface energy and so having the potential to hold more water on the surface. Clearly this is less important than crystal perfection because the crystalline samples have the lowest activation energy values. The Arrhenius-type plots that can be made for the effect temperature has on the absorption rate, Figures 6 and 7, reveal, from the negative activation

Table 4—Diffusivities Calculated from Thermogravimetric Balance Results

sample	temperature, °C	diffusivity $m^2 s^{-1} \times 10^{13}$
A	19.4	9.1
A	37.1	11.0
B	21.2	7.5
B	37.6	7.8
C	22.3	8.1
C	37.0	8.6

energy line, YZ, that two processes at least are involved in water uptake.

The physical form of the salt, whether crystalline or less-so, does affect the activation energy of the hydration process; when well-formed crystals are used, a smaller barrier to the process is encountered, compared to the poorly crystalline or amorphous forms. This suggests that the surface area is of less importance than some other feature in the mechanism, and if diffusion of water molecules into the solid is indeed dominant in controlling the rate of hydration, then the role of the crystal structure must be considered. Freer et al.⁹ have published the results of a single-crystal analysis of NS trihydrate, from which, in the structure features of sodium zeolites, can be seen in that sodium ions are accommodated within tunnels formed by cage like molecules. Diffusion as an activated process in such a structure is approached through a logarithmic analysis of the data.^{11,12} Given several assumptions, quoted in the references, a standard analysis leads to eq 1:

$$\frac{\Delta W}{W_{\infty}} = \frac{6(Dt)^{1/2}}{\pi r_c} \quad (1)$$

where D is the intracrystal diffusivity, r_c is the mean particle radius, assuming spherical particles and t is the elapsed time. Equation 1 predicts an essentially linear plot for square root time against $\Delta W/W_{\infty}$, and since most of the data presented here is linear between 20% and 80% reaction, the importance of diffusion is confirmed. Further analysis gives:

$$D = \frac{(\pi r_c \text{slope})^2}{36} \quad (2)$$

where the slope is that from the linear part of the $t^{1/2}$ against $\Delta W/W_{\infty}$ graphs and r_c is the average particle radius, taken here to be $2.5 \mu\text{m}$, as supplied by the manufacturers.

From eq 2, diffusivities at a range of temperature can be found from all the original experimental results, such as those shown in Figures 3–5. These data are given in Table 4 and show values at the lower end of the range reported for such systems as hydrocarbons diffusing into zeolites,¹² where values range between 10^{-8} to $10^{-13} m^2 s^{-1}$. This is evidence for a structurally related feature to be critically involved in the water absorption mechanism.

Data from Table 2 in Zhu et al.'s⁴ paper on dissolution of nedocromil magnesium enables us to compare both sets of experimental results in the following way:

An equation derived from the Noyes and Whitney's equation¹⁰ of dissolution from a solid surface into a liquid, is given as:

$$J = \frac{KDS}{h} \quad (3)$$

where J is the intrinsic dissolution rate, S is the solubility, D is the diffusivity into the solution, and h is the diffusion layer thickness.

Using the data for the nedocromil magnesium heptahydrate solubility⁴ and the diffusivity values for water vapor into NS crystals found in this work, K has a value of 20. It is a constant with no units and the value 20 comes from using SI units. Then using this value for K and a diffusion layer thickness of 1×10^{-6} m, with diffusivity data from Table 4 in this paper, we are able to predict a solubility for nedocromil magnesium decahydrate of 9.6 mol m^{-3} . This compares to $9.77 \times 10^{-3} \text{ mol L}^{-1}$, that is 9.77 mol m^{-3} , measured by Zhu et al.,⁴ which is in very close agreement and gives some confidence for the low values for diffusivity we have measured in the NS structure. Furthermore, for dissolution of the solid, it points to a situation where diffusion of water molecules into the crystal structure is as important as the Noyes and Whitney's approach involving diffusion of ions and molecules off the solid surface into the solution. This suggestion is given more credence by using the K value, already quoted above, with the diffusivity coefficient for 22 °C in Table 4 and applying them to eq 3, using $J = 0.0074 \text{ mol s}^{-1}/\text{m}^{-2}$, derived from data in Khankari et al., to predict the solubility of NS. A value of $3.7 \times 10^3 \text{ mol m}^{-3}$ is obtained. This value is in the same order of magnitude as that found experimentally by Khankari et al.; as $1.3 \times 10^3 \text{ mol m}^{-3}$. Furthermore, this model predicts an increased solubility for the anhydrous form of the drug, compared to the hydrates, because diffusivity into the crystal decreases as the degree of hydration increases. This is the order of solubility shown in Khankari et al.'s paper.

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