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Water vapor sorption by cephalosporins and penicillins

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Abstract

The sorption of water vapor by the sodium salts of ampicillin, nafcillin, ceftriaxone, cefazolin, piperacillin, cefotaxime and cefuroxime at 24, 34, 44 and 54°C was studied at vapor pressures between 5 and 100 torr by a new method (Hansen et al., 1996). Piperacillin absorbs water at all temperatures and vapor pressures studied. Cefuroxime and cefotaxime did not react. All the other compounds exhibited behavior consistent with formation of a new phase at some critical water vapor pressure, $P^{c}_{H_2O}$. Enthalpy changes for the water sorption reaction are calculated from a van't Hoff treatment of the $P^{c}_{H_2O}$ values. The thermodynamics of phase changes resulting from reactions of these compounds with water is discussed. The rate of water sorption is a linear function of the water vapor pressure at partial pressures above the equilibrium vapor pressure over the hydrated phase. Kinetics of water sorption as a function of temperature were measured. The activation energy for water sorption is approximately zero.

Keywords: Calorimetry; Water vapor; Sorption; Hydration; Kinetics; Cephalosporins; Penicillins

1. Introduction

One purpose of this study is to explore the advantages and limitations of the kinetic method for rapidly surveying reactions of materials with water vapor (Hansen et al., 1996). This method is not definitive when used alone, but because of the speed with which determinations can be made, is particularly applicable for quality control, for rapidly surveying rates and mechanisms of sorption reactions, and for obtaining data on materials difficult to study by equilibrium methods. The results in this paper illustrate what can be learned by application of this method.

Many drugs are decomposed by reaction with water. The cephalosporins and penicillins are well known examples where hydrolysis of the β-lactam ring results in loss of antibiotic activity. This process of decomposition under storage conditions begins with sorption of water vapor from the air. Thus, it is important to understand the sorption mechanism, thermodynamics and rate. A major purpose of this study is to examine the mechanism of sorption of water vapor by a series of sodium salts of penicillins and cephalosporins. It is presently unknown whether the hygroscopicity of these compounds is better described by an

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equilibrium isotherm with continuously variable binding energies, a phase transition to a stoichiometric hydrate, or a nonequilibrium kinetic model. Measurements made at equilibrium often cannot resolve such questions. For example, a previous equilibrium moisture content study (Wood et al., 1988) failed to resolve this question for sodium ampicillin.

Water vapor may be sorbed to a solid on binding sites with continuously variable energies in which case the sorption is properly described by a sorption isotherm in which the binding energy of an individual water molecule depends on the amount of reaction that has occurred. Physical sorption is usually described by this model because the binding constant depends on the fraction of surface covered. Chemical sorption can also follow this model if the product of the reaction with water is nonstoichiometric. The vapor pressure of water in equilibrium with such a system is a variable function of the total amount of both the sorbent and water in the system.

If a solid sorbent interacts with water vapor to form a new phase of invariant composition, either a hydrate or a saturated solution, the binding energy for water is constant, and the sorption is described by the thermodynamics of first-order phase changes. The hydrated phase will only exist above some critical water vapor pressure, P^cH_2O. Above P^cH_2O, three phases are present in the system, i.e. H_2O (g), anhydrous solid, and hydrate or saturated solution, and by the phase rule, the activity of all three must be invariant. Thus, the water vapor pressure in equilibrium with such a system is a constant (here labeled P^cH_2O) with all the properties of a thermodynamic equilibrium constant

There is actually a continuum of behavior between these two models for water sorption. Intermediate behavior is described with equations for higher-order phase transitions or by cooperative binding isotherm models. Such behavior indicates the presence of a hydrated phase of variable composition.

A further purpose of this study is to determine if the method used in this study to determine the equilibrium vapor pressure can also be used to determine the crystallinity of materials. The minimum vapor pressure of water at which a new phase, either a hydrate or saturated solution, can form depends on the difference in the Gibbs free energies of the sorbent and the hydrated phase. Because the amorphous form of a material may have a different free energy than the crystalline form, the two forms may have different equilibrium water vapor pressures (P^cH_2O). The higher the free energy of the sorbent, the lower the water vapor pressure required for stability of the hydrated phase. Equilibrium methods for determination of P^cH_2O usually do not detect the difference because the less stable sorbent phase is converted to the more stable phase in the course of the experiment. But kinetic methods should be sensitive to the free energy difference between amorphous and crystalline forms. The kinetic method described in Hansen et al. (1996) detects the critical water vapor pressure P^cH_2O as a change in $d\phi/dPH_2O$ where ϕ is the rate of heat produced by the sample (proportional to the rate of water sorption) and PH_2O is the vapor pressure of water in contact with the sample. In this method, PH_2O is continuously varied from well below to well above P^cH_2O. The change in $d\phi/dPH_2O$ thus occurs at the PH_2O value at which the hydrated phase just begins to form, and the free energy of the sorbent should affect this value.

2. Materials and methods

2.1. Materials

Ampicillin sodium (Wyeth), nafcillin sodium (Wyeth), ceftriaxone sodium (Roche), cefazolin sodium (crystalline, Lark; crystalline, Dobfar; and lyophilized, Dobfar), piperacillin sodium (Lederle), cefotaxime sodium (Hoechst), and cefuroxime sodium (Glaxo) were stored at 5°C in a desiccator with Drierite. The samples were allowed to warm to room temperature before opening to avoid water condensation. The two Dobfar lots of cefazolin sodium were verified to be respectively highly crystalline and amorphous by X-ray diffraction (Sebhatu et al., 1994).

2.2. Methods

The equipment and methods used for determination of water vapor sorption kinetics and thermodynamics are described in a previous paper (Hansen et al., 1996). Heats of solution were measured in a Hart Scientific model 4310 solution calorimeter.

3. Results

Fig. 1 shows how P^cH_2O values and endpoint widths were obtained from plots of the measured heat rate versus the water vapor pressure in contact with the sample. The plots are considerably more rounded in the vicinity of P^cH_2O for the compounds in this study than for the inorganic compounds previously studied (Hansen et al., 1996). Of the antibiotics studied, ampicillin and cefazolin have the most rounded endpoints.

Figs. 2 and 3 graphically show the results of one experiment on ampicillin and nafcillin at each temperature. No baseline correction has been subtracted from the data as shown. Ampicillin shows one very rounded endpoint at all temperatures studied. Nafcillin shows two endpoints at all four temperatures. Cefazolin acts similarly to ampicillin. Data for cefuroxime and cefotaxime are indistinguishable from baseline data at all temperatures. Piperacillin appears to react with water vapor at all vapor pressures and temperatures tested, i.e. P^cH_2O < 15 torr at 24°C and 34°C and < 20 torr at 44°C and 54°C. Ceftriaxone exhibited two definite endpoints (similar in appearance to the curves for nafcillin in Fig. 3) at 44°C and 54°C, possibly two at 34°C, but only one at 24°C. As explained in Hansen et al. (1996), the first endpoint for nafcillin and ceftriaxone is for reaction of a surface impurity or formation of a solid hydrate and the second endpoint for formation of the saturated solution or a higher hydrate.

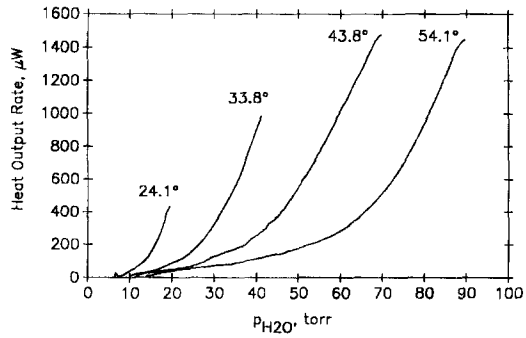

Fig. 2. Example data sets for sodium ampicillin.

Table 1 gives the P^cH_2O values, endpoint widths and van't Hoff $\Delta H°$ values calculated from the temperature dependence of P^cH_2O values. Fig. 4 shows van't Hoff plots of the P^cH_2O data. The linear plots obtained confirm that the data have not been misinterpreted, e.g. the van't Hoff plot for the first endpoint of ceftriaxone shows that this endpoint was not observed at 25°C because P^cH_2O is too low to measure by this method. The results obtained were independent of sample size and scan rate within the instrument limitations as previously discussed (Hansen et al., 1996).

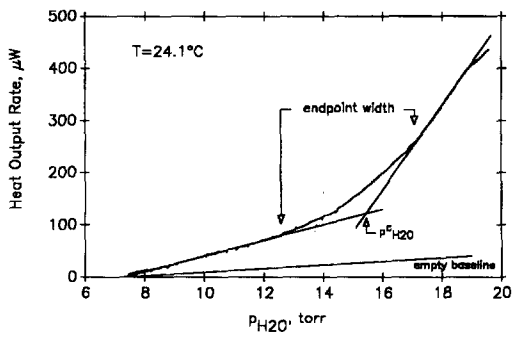

Fig. 1. Data set for ampicillin illustrating the determination of P^cH_2O and endpoint width.

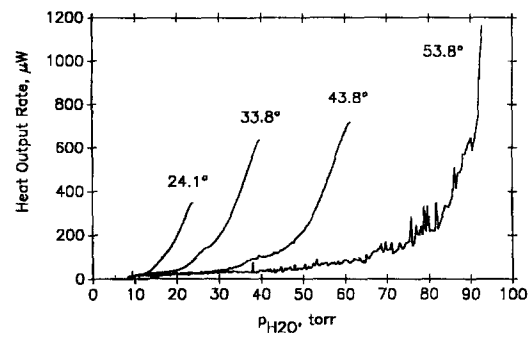

Fig. 3. Example data sets for sodium nafcillin.

Table 1
Critical water vapor pressures and reaction endpoint widths for the sodium salts of ampicillin, nafcillin, ceftriaxone and cefazolin

T, °C	$P^c_{H_2O}$, torr[a]		Endpoint width torr[a]	
	First endpoint	Second endpoint		
Ampicillin				
24	15.7 ± 0.2 (4)		8 ± 2 (4)	
34	26.0 ± 1.6 (4)		15 ± 3 (4)	
44	39 ± 2 (3)		16 ± 6 (3)	
54	63 ± 2 (4)		28 ± 7 (4)	
	$\Delta H°$ = −38kJ/mol H_2O			
Nafcillin				
24	13.8 ± 0.6 (2)	18.7 ± 0.3 (2)	2 ± 1 (2)	2 ± 1 (2)
34	22.2 ± 0.9 (3)	30.8 ± 1.0 (3)	5 ± 1 (3)	5 ± 1 (3)
44	33 ± 0.7 (3)	49 ± 1 (4)	4 ± 2 (3)	12 ± 1 (4)
54	45 ± 1 (4)	74 ± 1 (4)	1 ± 1 (4)	4 ± 2 (4)
	$\Delta H°$ = −32 kJ/mol H_2O	$\Delta H°$ = −37 kJ/mol H_2O		
Ceftriaxone				
24	—	18.5 ± 0.7 (3)	—	4 ± 1 (3)
34	23 ± 1 (3)	34 ± 1 (3)	1 ± 1 (3)	1 ± 1 (3)
44	38 ± 6 (2)	57 ± 0.5 (2)	1 ± 1 (2)	3 ± 1 (2)
54	48 ± 2 (3)	78 (1)	0 (3)	0 (1)
	$\Delta H°$ = −31 kJ/mol H_2O	$\Delta H°$ = −39 kJ/mol H_2O		
Cefazolin (Lark, crystalline)				
24	<12 (2)		—	
34	23 ± 0.5 (3)		8 ± 1 (3)	
44	34 ± 1 (3)		9 ± 2 (3)	
54	61 ± 6 (2)		25 ± 5 (2)	
	$\Delta H°$ = −41 kJ/mol H_2O			
Cefazolin (Dobfar, crystalline)				
25	–		–	
35	22 ± 1 (5)		7 ± 2 (5)	
45	33 ± 1 (3)		6 ± 1 (3)	
55	51 ± 2 (2)		19 ± 1 (2)	
	$\Delta H°$ = −35 kJ/mol H_2O			
Cefazolin (Dobfar, amorphous)				
25	–		–	
35	21 ± 1 (4)		3 ± 1 (4)	
45	32 ± 1 (2)		6 ± 4 (2)	
55	53 ± 2 (2)		22 ± 1 (2)	
	$\Delta H°$ = −39 kJ/mol H_2O			

[a]Uncertainties are given as the standard deviation of the mean of the number of data points given in parentheses.

The $P^c_{H_2O}$ data obtained on ampicillin in this study agree with the data obtained from an equilibrium moisture content study (Wood et al., 1988). Fig. 5 compares the results from these two studies. The previous study probably underestimated $P^c_{H_2O}$ because data were collected at discrete water vapor pressures. The value of $P^c_{H_2O}$ was estimated by extrapolation and interpolation between data points, a procedure that probably underestimated the actual values because of the distribution of data points obtained. The study reported here measured $P^c_{H_2O}$ corresponding to the onset of the sorption reaction, a procedure that overestimates $P^c_{H_2O}$ if the reaction is slow

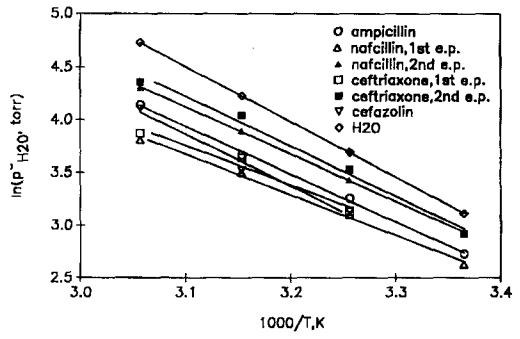

Fig. 4. van't Hoff plots of ln $P^{c}H_2O$ against reciprocal absolute temperature for the compounds studied and for comparison, H_2O. Data for pure water are from Weast (1974).

compared to the rate of change of $P^{c}H_2O$ during the experiment. Too high a scan rate can also result in a negative temperature error in the water in the scanning block and thus would result in a positive error in $P^{c}H_2O$. No systematic effect of scan rate was seen, so the error from these sources cannot be large, but small systematic errors would nevertheless be in a positive direction. These systematic errors in both studies may account for the small, but systematic differences seen in Fig. 5. Decomposition of the sample during the long exposures to water in the equilibrium moisture content measurements could also be a source of error in those measurements.

Table 2 reports the equilibrium vapor pressure in terms of relative humidity, h_r^c. There is a small decrease in h_r^c with temperature for ampicillin, nafcillin (both reactions), and possibly for ceftriaxone and cefazolin; consistent with a small endothermic enthalpy change for the hydration reactions with liquid water (Hansen et al., 1996).

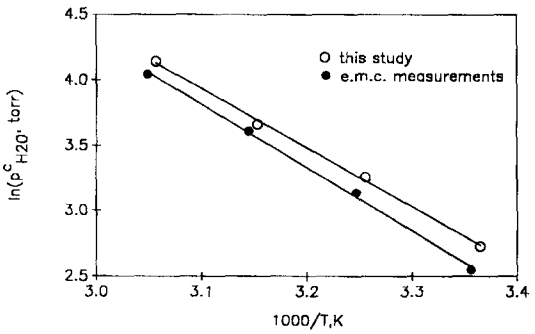

Fig. 5. Comparison of $P^{c}H_2O$ data from this study and from an equilibrium moisture content study on ampicillin sodium (Wood et al., 1988).

Kinetic data were also obtained as previously described (Hansen et al., 1996). Table 2 gives the $kA\Delta H$ values obtained from the slopes of ϕ versus PH_2O plots. In all cases the activation energy is approximately zero.

To test the ability of the kinetic method to determine crystallinity, two samples of cefazolin sodium from the same manufacturer, one crystalline and the other amorphous, were studied. Table 1 gives the results for $P^{c}H_2O$ and the endpoint width obtained on these samples. Neither the endpoint width nor the $P^{c}H_2O$ values are significantly different for the crystalline and amorphous materials. The results are also in agreement with the results on the sample of cefazolin sodium from Lark. The kinetics of water sorption are also the same for the crystalline and amorphous materials, Table 2. Enthalpy changes were also measured at 25°C for solution in water of the Dobfar lots of amorphous (-0.22 ± 0.08 (2) J g^{-1}) and crystalline ($+1.27 \pm 0.06$ (2) J g^{-1}) sodium cefazolin.

4. Discussion

The lot of piperacillin used in this study may be an example of a material in which the amount of water sorbed depends only on the exposure time and water vapor pressure, i.e. water is simply sorbed at a rate proportional to the water vapor pressure in contact with the material. If PH_2O is high enough, at some point in time sufficient water will be sorbed to form a liquid phase, i.e. deliquescence may be exhibited.

If the hygroscopic behavior of a material is the result of a first-order phase change, there will be no change in the composition of the sample unless the Gibbs free energy change (ΔG) is less than zero. Since ΔG for the reaction depends on water vapor pressure, under conditions of increasing water vapor pressure, the new phase will first appear at the water vapor pressure where ΔG equals zero, i.e. at $PH_2O = P^{c}H_2O$. At $PH_2O > P^{c}H_2O$, the hydrated phase becomes the thermody-

Table 2
Kinetics of H_2O (g) uptake by the sodium salts of ampicillin, nafcillin, ceftriaxone, and cefazolin

Temperature°C	Critical relative humidity[a] $h_r^c = P^cH_2O/P^{sat}H_2O$, %		Preslope[b,c] $kA\Delta H = d(\phi,\mu W)/d(PH_2O, torr)$	Postslope[b,d]	
	First endpoint	Second endpoint		First endpoint	Second endpoint
Ampicillin					
24	69.7 ± 0.1		4.7 (1)	80 (1)	
34	65 ± 4		2.9 ± 0.6 (4)	73 ± 8 (4)	
44	57 ± 3		1.4 ± 0.9 (3)	75 ± 10 (3)	
54	56 ± 2		2.0 ± 0.7 (2)	48 ± 8 (2)	
Nafcillin					
24	61 ± 3	83 ± 1	6.2 ± 2.4 (2)	25 ± 2 (2)	45 ± 0 (2)
34	56 ± 2	77 ± 3	1.3 ± 0.2 (3)	17 ± 2 (3)	49 ± 5 (3)
44	49 ± 1	72 ± 2	1.0 ± 0.1 (4)	23 ± 5 (2)	58 ± 7 (4)
54	40 ± 1	66 ± 1	1.8 ± 0.4 (4)	6.2 ± 0.6 (4)	30 ± 7 (4)
Ceftriaxone					
24	–	82 ± 3	–	12 ± 2 (3)	51 ± 1 (3)
34	58 ± 3	86 ± 3	5.3 ± 0.4 (3)	9 ± 2 (3)	37 ± 3 (3)
44	56 ± 9	84 ± 1	1.6 ± 0.5 (2)	5.5 ± 0.7 (2)	48 ± 1 (2)
54	43 ± 2	70	2.7 ± 0.8 (3)	6 ± 1 (3)	6 (1)
Cefazolin (Lark, crystalline)					
24	<53		–	32 ± 3 (2)	
34	58 ± 1		15 ± 4 (3)	51 ± 4 (3)	
44	50 ± 2		10 ± 2 (3)	72 ± 7 (3)	
54	54 ± 5		7.8 ± 0.1 (2)	47 ± 6 (2)	
Cefazolin (Dobfar, crystalline)					
25	–		–	34 (1)	
35	53 ± 2		34 ± 1 (5)	46 ± 2 (5)	
45	47 ± 1		31 ± 0 (2)	43 ± 1 (2)	
55	44 ± 2		18 ± 1 (3)	34 ± 5 (3)	
Cefazolin (Doblar, amorphous)					
25	–		–	34 ± 1 (2)	
35	51 ± 2		30 ± 5 (3)	46 ± 3 (3)	
45	45 ± 1		25 ± 2 (2)	38 ± 6 (2)	
55	45 ± 2		13 ± 3 (2)	38 ± 3 (2)	

[a]Calculated from data in Table 1.
[b]Uncertainties are given as the standard deviation of the mean of the number of data points given in parentheses.
[c]Slope below the critical relative humidity.
[d]Slope above the critical relative humidity.

namically stable phase. Fig. 6 graphically illustrates these concepts. At water vapor pressures above P^cH_2O, three phases are present and the water vapor pressure must be constant if the system is at equilibrium. If the water vapor pressure exceeds P^cH_2O, the excess will react to produce more of the hydrated phase. The rate of reaction will be proportional to $(PH_2O - P^cH_2O)$.

Ampicillin, nafcillin, ceftriaxone and cefazolin exhibited behavior consistent with formation of a new phase at a critical water vapor pressure. Although not nearly as sharp as those for inorganic compounds (Hansen et al., 1996), the slope changes in the curves in Figs. 2 and 3 clearly demonstrate the presence of phase changes in these systems. The lack of dependence of the P^cH_2O value on the scan rate shows that this is an equilibrium sorption and not a slow process that would ultimately lead to deliquescence at vapor pressures below the measured P^cH_2O.

If P^cH_2O is indeed an equilibrium vapor pressure over a hydrated phase, then the temperature

dependence will be given by the van't Hoff equation.

$$d(lnP^{c}_{H_2O})/d(1/T) = \Delta H°/R \quad (1)$$

The linearity of the plots of ln $P^{c}H_2O$ against the reciprocal of the absolute temperature shown in Fig. 4 is thus further evidence for the phase change mechanism of reaction of ampicillin, nafcillin, ceftriaxone and cefazolin.

Furthermore, the value of $\Delta H°$ calculated from the slope of a van't Hoff plot should be equal to the sum of the heat of condensation of water and either the heat of solution in the case of formation of a saturated solution or the heat of formation of the hydrate from liquid water and the anhydrous compound in the case of formation of a solid hydrate. All of the $\Delta H°$ values measured in this study are less negative than $\Delta H°$ for condensation of water (-44.0 kJ mol^{-1}) (Wagman et al., 1982). The $\Delta H°$ values are thus in agreement with the prediction from the phase change mechanism if $\Delta H°$ for solution of the compounds to form a saturated solution or for formation of a hydrate is endothermic and in the range of 0–15 kJ/mol H_2O. This conclusion is consistent with our data on the heat of solution of cefazolin sodium and with literature data on heats of solution of cefazolin and related compounds at infinite dilution. Note that the van't Hoff $\Delta H°$ is the heat of solution in saturated solution while the calorimetric $\Delta H°$ is the heat of solution in dilute solution.

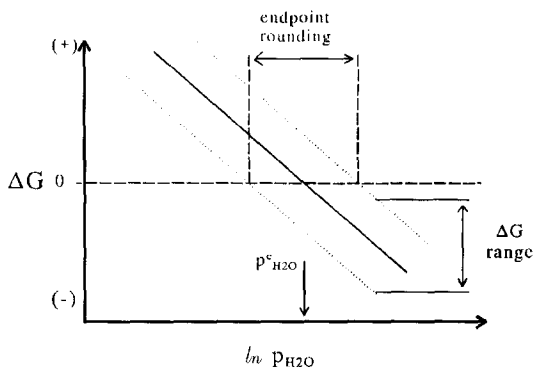

Fig. 6. Graphical illustration showing how the range in the Gibbs free energy change (ΔG) for the hydration reaction is related to endpoint rounding.

Literature data on these compounds show $\Delta H°$ values in water are near zero (Pikal et al., 1978) and vary considerably with state of hydration and crystallinity (Pikal et al., 1978; Pikal and Dellerman, 1989). Furthermore, the heat of formation of hydrates from liquid water has been shown to be small compared to the heat of condensation of water for ampicillin free acid and a variety of other, similar compounds (Khankari et al., 1992).

The change in slope, i.e. $d\phi/dP_{H_2O}$, observed for the compounds in this study occurs over a range of 3–30 torr for ampicillin and cefazolin, 2–12 torr for both nafcillin endpoints, and 1–4 torr for ceftriaxone (both endpoints). The endpoint width tends to increase with temperature in ampicillin and cefazolin, but not in ceftriaxone and nafcillin. In an exactly first-order transition, there would be no endpoint rounding. The endpoints observed in the inorganic systems examined in another study (Hansen et al., 1996) were close to the ideal model.

There are four possible explanations for a rounded endpoint. (a) The reaction could be slow compared to the rate of change of P_{H_2O}. The lack of dependence of $P^{c}H_2O$ and endpoint width on scan rate shows this not to apply to any of the compounds in this study. (b) Variation in particle size could cause a significant variation in ΔG for the hydration reaction if the surface free energy is significant. (c) If the materials are partially amorphous, ΔG may not be a constant, and the higher energy material will react before the lower energy material in the sample (Pikal et al., 1978). (d) If the phase transition is higher than first order, it will occur over a range of water vapor pressure. For example, formation of a nonstoichiometric hydrate would result in a higher-order transition between the phases. The last three explanations all involve a variation of ΔG with the extent of reaction as illustrated in Fig. 6. If explanations (a) and (d) are applicable, the amount of endpoint rounding will be temperature dependent, but since the properties of the sorbent, i.e. particle size and crystallinity, are independent of temperature, endpoint rounding caused by (b) or (c) will be independent of temperature.

The presence of amorphous material or a variation in surface free energies of the particles in the

samples probably accounts for the temperature independent endpoint rounding in nafcillin and ceftriaxone and may partially account for the endpoint rounding in ampicillin and cefazolin. The temperature dependence of the endpoint rounding in the latter two compounds additionally suggests the formation of a nonstoichiometric hydrate near the P_{H_2O} required for formation of the saturated solution.

There are two possible reasons why no difference was seen between the amorphous and crystalline cefazolin. (a) The amorphous material may crystallize before $P^c_{H_2O}$ is reached in the experiment. However, if this reaction had occurred, it would have been seen in the calorimetric sorption data as a difference between the amorphous and crystalline materials, and can therefore be ruled out. (b) The Gibbs free energy of the amorphous cefazolin may not be significantly different from or may even be more positive than that of the crystalline material. The enthalpy change for crystallization of the amorphous cefazolin, $+1.05$ J g^{-1} as obtained from the heats of solution (Section 3), is definitely endothermic. Because ΔH for crystallization is endothermic and ΔS must be negative for this ordering process, ΔG ($= \Delta H - T\Delta S$) for crystallization of this material must be positive, i.e. crystallization of the amorphous cefazolin is not a spontaneous process at 25°C. Thus, explanation (b) apparently explains the failure of the water vapor scanning method to find a crystallinity related difference. Both of the explanations for the failure to see a difference in $P^c_{H_2O}$ are material specific, i.e. they do not apply in general to all materials. Thus, the theory discussed in the introduction is still valid. The failure to demonstrate the utility of the method with one material does not mean it will not work with other materials. Like all of the other methods for crystallinity determinations, this one is not completely general.

5. Conclusion

The methods used in this paper are useful for rapidly surveying a series of materials for their reaction with water vapor. The results obtained are informative and valuable, but because they do not contain information on the stoichiometry of the reaction, need to be combined with results from a variety of other kinds of studies before the description of the reaction with water can be considered definitive. The method described here may be particularly useful when measurement of the equilibrium water vapor pressure or equilibrium moisture content is impractical or uncertain because of irreversible degradation of the drug by lengthy exposure to water.

The particular lots of cefuroxime and cefotaxime used in this study are not hygroscopic at any of the conditions studied. The ampicillin, nafcillin, cefazolin and ceftriaxone samples used in this study have well defined $P^c_{H_2O}$ values that establish packaging and storage conditions for the bulk, raw drug and solid dosage forms. The shelf-life of the piperacillin lot will depend on how much water is available to be sorbed under the storage conditions. The first endpoint observed for nafcillin and ceftriaxone shows the presence of hydrates or surface impurities on these materials that have not previously been observed or characterized. The mechanism of water sorption by ampicillin, nafcillin, cefazolin and ceftriaxone clearly is closer to a phase change than to a continuous sorption model.

The kind of data collected in this study should be useful in selecting storage conditions, container materials and designs, and excipients for formulations to maximize stability and shelf-life of pharmaceuticals. Since sorbed water also affects the handling properties of bulk powders, this type of data should also be useful in planning manufacturing processes.

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