AN APPROACH TO THE EVALUATION OF HYGROSCOPICITY FOR PHARMACEUTICAL SOLIDS

BY

LYNN VAN CAMPEN

A thesis submitted in partial fulfillment of the
requirements for the degree of

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AN APPROACH TO THE EVALUATION OF HYGROSCOPICITY FOR PHARMACEUTICAL SOLIDS

Lynn Van Campen

Under the supervision of
Professor Jens T. Carstensen
and
Professor George Zografi

Hygroscopicity plays a significant role in many formulation problems. Uncontrolled moisture sorption can lead to chemical degradation of active ingredients or to undesirable physical characteristics of the total solid dosage formulation. Yet hygroscopicity remains poorly defined in a quantitative sense. The object of this study was to construct an apparatus capable of measuring accurately and sensitively the rapid moisture uptake by hygroscopic materials. In so doing it was hoped that observed hygroscopicity could be correlated with specific physical or chemical properties of the compounds, and that one or more parameters could be determined which would quantitatively define hygroscopic behavior.

It was proposed that the driving force for moisture adsorption is comprised of two factors: the total surface area of the sample and the pressure difference between the water vapor pressure in the atmosphere and that prevailing over a saturated solution of the substance. It was further proposed that a proportionality constant, k, characteristic of the adsorbing material, mediates the effectiveness of that driving force. This relation has been set forth on infrequent occasion in the literature, but little data has been provided either to support or disprove its validity.

A vacuum manifold within which an electronic microbalance could be operated was constructed and then used to monitor in vacuo moisture adsorption gravimetrically. Preliminary experiments suggested that certain design modifications were necessary, however, to achieve better stability of and control over atmospheric relative humidity, which was critical to the collection of meaningful data. Appropriate modifications of the apparatus were made and appear to have successfully maximized the experimental potential of the instrument.

The modified adsorption apparatus was used to study the water vapor adsorption behavior of choline chloride, choline bromide and choline iodide. The nature of their sorption was consistent with the proposed model, i.e. their initial rates of adsorption were constant with time and were linearly related to atmospheric relative humidity. A plot of adsorption rate as a function of relative humidity demonstrated the general validity of these relationships. The slope and intercept of this curve appeared to be appropriate parameters for defining uniquely the hygroscopicity of a given system. Increasing hygroscopicity is then associated with increasing slope (k) and decreasing intercept (critical relative humidity or RH_o) values. On this basis the hygroscopicity of the choline halide series decreased in the order chloride > bromide > iodide. Furthermore the calculated k values correlated directly with estimated molar solubilities. It was therefore suggested that solubility is one of the primary factors controlling hygroscopic behavior.

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INTRODUCTION

Understanding the nature of moisture adsorption by pharmaceutical substances has long been recognized as an important, and usually formidable, task of the solid dosage formulation chemist. For a drug that degrades in the presence of water, characterization of both the equilibrium moisture content (EMC) of the formulated material as well as the rate at which this level is achieved is imperative. These properties are often referred to as the "hygroscopic" properties of the substance, a term not clearly defined, but implying both kinetic and thermodynamic criteria of behavior. Often "trial and error" approaches are necessarily taken by the formulator to develop a successful formulation for a drug subject to moisture effects detrimental to its stability. Were the actual mechanisms controlling hygroscopic phenomena better understood, the frequently encountered problems of chemical (drug) and physical (formulation) instability induced by moisture could be systematically avoided.

One of the first studies examining the factors determining hygroscopic behavior is that by Edgar and Swan (1) in 1922. They predicted *a priori* that the rate of moisture adsorption could be expected to depend on (1) the difference between the partial pressure of water vapor in the atmosphere and that above the saturated aqueous solution of the hygroscopic substance, (2) temperature, (3) surface area of the solid exposed to the water vapor, (4) "velocity of movement" of the moist air and (5) a "reaction constant" characteristic of the solid under study. Their first step in understanding the phenomenon of hygroscopicity, however, was to study the equilibrium vapor pressures of the saturated aqueous solutions rather than to attempt obtaining rate data. Unfortunately, their intended follow-up kinetic studies either never materialized or were never reported.

Pharmaceutical attention to the definition and control of hygroscopic behavior was minimal until 1949 when Griffin et al. (2) published a landmark article on the use of humectants in cosmetic formulations. They attempted here to lay a foundation of terms and definitions to describe hygroscopicity and thereby better define the manner in which humectants exert their desired effects on a formulation. The three basic terms they introduced are (1) "equilibrium hygroscopicity" -- the state or condition that exists when an aqueous solution neither gains nor loses moisture at a given relative humidity (RH); (2) "dynamic hygroscopicity" -- the rate with which a substance or its aqueous solution gains or loses water while approaching equilibrium (expressed only as a relative quantity); and (3) "volatility" -- the tendency of a product to evaporate. These authors further suggested that the factors governing the latter two kinetic properties include sample thickness (relating to available surface area) and "inherent rate" of the product, as well as RH and temperature.

Attempts to control the degradative effects of moisture on various pharmaceuticals by using effective packaging techniques were later discussed by Yamamoto and Takahashi (3). They quantified the moisture gain (or loss) rate dependence alluded to in the aforegoing discussion, proposing that

$$W = Kt(P_a - P') \qquad \text{Eq.(1)}$$

where W = sample weight gain per unit area of effective surface area, K = a proportionality constant, t = time, P_a = water vapor pressure of the external atmosphere, and P' = water vapor pressure over the saturated solution of the substance. They implied that the packaging of the product influenced only K which they termed the "moisture transmission factor of the container".

More recently Carstensen (4) utilized the same relation as given in Eq. (1), but in differential form where he allowed the rate, γ, to equal dW/dt, and where W is now the weight of the moisture-adsorbing powder, no longer normalized to unit surface area. On integration and conversion to relative humidities (where $RH = 100 \cdot P/P_o$, P_o = vapor pressure of pure water at the given temperature), one obtains:

$$\gamma = kAP_o(RH_i - RH_o) \qquad \text{Eq.(2)}$$

where RH_i = relative humidity of atmosphere during the course of the experiment, RH_o = relative humidity prevailing over a saturated solution of the substance, often termed the "critical relative humidity" (CRH), and where K has been separated into a new proportionality constant, k, multiplied by the total surface area of the sample, A. Carstensen further proposed that initial rates will be constant, i.e. weight gains (or losses) are initially linear, varying in slope depending on RH_i. It then follows from the above arguments that when $RH_i = RH_o$, the rate of moisture uptake will be zero. If a plot of $\gamma_{initial}$ versus RH_i is prepared, a straight line should result whose x-intercept ($\gamma = 0$) should represent RH_o.

In demonstrating the validity of these relations, Carstensen used the familiar technique of storing samples in desiccators wherein saturated aqueous solutions of various inorganic salts (of known RH_o values at room temperature) had been allowed to equilibrate, providing the experimental RH_i. Periodic and successive withdrawal and weighing of the samples result in the collection of the desired rate data. There are many unassessable and uncontrollable variables inherent in this "desiccator storage" method, however, which render it unsuitable for accurate kinetic determinations of moisture uptake by highly hygroscopic materials. It is thus desirable to develop some experimental means of resolving these variables which govern moisture sorption rates, and thereby obtain a sensitive and theoretically meaningful measurement of initial adsorption rates from which mechanistic conclusions can be drawn.

STATEMENT OF PURPOSE

The primary objective of this study was to design an apparatus capable of rapid, sensitive, and accurate response to initial moisture adsorption onto hygroscopic materials. Secondly, the effective operation of the instrument was to be verified by studying substances of pharmaceutical interest, wherein the validity of the general kinetic relations set forth in the preceding "Introduction" could be tested, i.e. that

(i) $\gamma \propto RH_i - RH_o$,

(ii) $\gamma_{initial}$ = constant

and (iii) $\gamma = 0$ when $RH_i = RH_o$.

REVIEW OF THE LITERATURE

An exhaustive review of the literature on adsorption would readily find one engulfed in a seemingly infinite set of multidimensional "factorials" with respect to experimental conditions, goals, materials, methods. The subject can be compartmentalized in a variety of ways, e.g. solid/liquid or solution/vapor or gas phase, aqueous/nonaqueous adsorbate, adsorbate-soluble/-insoluble adsorbent, kinetic/equilibrium processes, and porous/nonporous solids. It is the purpose of this review, however, only to point in the right direction of appropriate literature covering the more general aspects of adsorption, then to concentrate on the "corner" of this factorial relevant to the kinetics of moisture adsorption as it relates to the pharmaceutical area. Table I provides a categorized summary of general adsorption literature, including for the most part either "classic articles" or work representative of very recent efforts in the field. While Table I is hardly complete in coverage, it does illustrate the disparity of attention given equilibrium vs. kinetic studies. Hidden within this Table are those few papers in which an attempt was made to characterize the phenomenon of hygroscopicity. These

TABLE I. SUMMARY OF GENERAL ADSORPTION LITERATURE REFERENCES

	EQUILIBRIUM	KINETIC
THEORETICAL		
Texts and reviews	5-13	13-17
Research articles	10,18-44	9,22,23,37,45-63
B.E.T.	5,8,13,18,36,64	
EXPERIMENTAL		
Adsorption from solution	65-73	21,45,46,65,66,68,74,75
Non-aqueous adsorbates	30,31,33,50,57,76-103	50,104-110
Water vapor adsorption		
General; at interfaces	111,112	
Nucleation, condensation	111,113-116	117-119
Water-insoluble adsorbents:		
Silicaceous materials; Zeolites, clays	22,120-135	22,51,136,137
Miscellaneous inorganic	24,111,138-155	156
Organic,biological, macromolecular substrates	135,157-187	157,185,188
Water-soluble adsorbents:		
Inorganic	1,181,189-213	189,195,202,203,214,215
Organic	178,179,181,182,216-221	
Bulk properties; composites, powders	193,198,218,219,222-227	

deserve further comment.

Many materials of commercial interest are affected by the detrimental effects of uncontrolled moisture adsorption, such as fertilizers, foods, fibers, textiles and woods. Adams and Merz (212) attempted to predict the storage and handling properties of fertilizer salts by measuring their mixtures' hygroscopicity, which they defined as the maximum humidity in which the material could exist without becoming "moist" -- clearly a thermodynamic condition. Using an isoteniscope, they determined the vapor pressures of saturated solutions of pure salts and of two-component mixtures as a function of temperature. They observed that the hygroscopicity of the mixtures was generally greater than that of the more hygroscopic constituent, unless the components reacted to form a compound or double salt of lower hygroscopicity (i.e. greater vapor pressure). The work by Edgar and Swan (1), cited previously, was conducted with similar intent on many of the same salts. In a similar study, Browne (216) failed to show any fixed relationship between the EMC's of various carbohydrates and their chambers' RH's.

Later in 1945 Griffin (167) alluded to the significance of <u>rates</u> of moisture uptake in a study of glues, but considered only equilibrium studies feasible at that time. He proceeded to investigate the hygroscopicity, defined for his purpose as EMC's at varying RH's, of a typical glue softened with various mixtures of sorbitol and glycerol. Again, the hygroscopicities of the individual components were not additive, especially at low RH's. His later studies with humectants (2), already discussed in some detail, dealt more directly with the aspect of the rate processes involved, and in fact, presented a substantial amount of kinetic data. At about the same time, Yee and Davis (211) developed an "accelerated method" for determining the EMC's of various inorganic salts and fertilizers. They reduced the time required to reach equilibrium via modifying the sample preparation and by agitating the atmosphere within the constant-RH test chamber. The authors also collected sorption rate data in an effort to measure systematically, if perhaps only grossly, the effects of bed depth, number of samples per chamber, sample container size, and temperature on uptake rate. This is perhaps the first such rate data so collected.

Emphasizing the experimental elusiveness of the kinetic aspects of hygroscopicity, Markowitz and Boryta (213) more recently proposed the theoretical suitability and experimental advantage of the thermodynamic approach. They chose as a criterion for hygroscopicity the negative value of the free energy change accompanying the transfer of water to the condensed (adsorbed) phase from the atmosphere, as driven by the imbalance of chemical potential of water between the two systems. They term the -ΔG value the "hygroscopicity potential" (HP) as given by:

$$HP = -\Delta G = \mu_{H_2O,pure} - \mu_{H_2O,sys} = RT \ln\left(\frac{P_{H_2O,pure}}{P_{H_2O,sys}}\right) \quad \text{Eq.(3)}$$

Acknowledging the kinetic character of the hygroscopic process, the authors claim only that such thermodynamic measurements "will probably allow some insight" into the rate processes involved, "especially for systems in which a saturated solution results" on water uptake. They referred to the "chemical reaction" nature of hygroscopicity, that is, the fact that it is characterized by a thermodynamic driving force and a kinetic rate. They further declared that the "customary kinetic experiment" is unable to resolve the individual factors upon which this rate depends, and is therefore of little theoretical significance. Their experimental results included calculation of the HP values for various saturated inorganic salt solutions at various temperatures.

Another thermodynamic correlation was later discussed by Admirat and Grenier (214) in which the CRH values of hygroscopic salts at low temperatures were shown to correspond to eutectic data. This enabled the authors to express the CRH's for the salt-water systems as three-dimensional

P-T-x diagrams.

A kinetic study of the hygroscopicity of water-soluble salts and mineral fertilizers was undertaken, however, by Kuvshinnikov et al. (215), who recognized the inadequacy of the pure thermodynamic approach. They defined a "hygroscopicity coefficient" as the logarithm of the initial slope of the kinetic curve of moisture uptake. They described the sorption curves by the relation:

$$W = W_{\infty} (1- e^{-kt}) \qquad \text{Eq. (4)}$$

where W = moisture content, W_{∞} = equilibrium moisture content, and k = constant of uptake. They obtained good agreement between their experimental and theoretical curves. Using the same "hygroscopicity coefficient" Panidi et al. (203) evaluated the moisture uptake of various double sodium potassium phosphate salts. Their coefficients were all determined at a constant 81% RH. From their results they attempted to infer structural characteristics of the mixed salts.

Another approach to the study of moisture adsorption kinetics is that typified by the work of Onischak and Gidaspow (202). The purpose of their study was to determine the mechanism of water vapor sorption by anhydrous LiCl, sufficiently rapid that it was assumed to be gas diffusion-controlled. Using what is often referred to as a "dynamic" rather than a "static" method, these authors monitored the moisture content of inlet and outlet air streams flowing through a parallel plate reactor which contained a compressed bed of the salt. Appropriate diffusion conditions and boundary values were assigned. Comparing theoretical and observed data, they concluded that the rate-controlling step may be the formation of the solution which then must diffuse into the dry salt matrix, and that equilibrium conditions cannot be assumed to prevail at the surface of the salt.

Addou and Vast (195) investigated the hygroscopicity of various pure and mixed potassium salts by passing humid air through a column of the salt and measuring weight uptake as a function of column length. They proposed that the weight uptake profile with length and its development with time correlated with salt hygroscopicity. From the profiles collected, they concluded that moisture is first chemisorbed, followed by dissolution of the salt on the surface of each crystal leading to saturation, and that, in the case of mixed salts, actual ion displacement can occur.

The pharmaceutical corner of adsorption literature, not listed in Table I, is limited in quantity, and, in keeping with the general literature trend, is almost wholly concerned with equilibrium measurements. The practical implications of hygroscopicity in the formulation of medicinals falls into two primary categories: (1) the chemical instability imparted to many drugs by moisture and (2) the changes in bulk properties of drug formulations effected by moisture. In his review of methods for determining water content in pharmaceutical materials, Johnson (228) addressed these problems in some detail. He also described the various forms water can assume in pharmaceutical materials, from "free liquid" to varying degrees of "bound" water.

As discussed earlier, the first pharmaceutical studies of hygroscopicity involved the systematic evaluation of effective humectant incorporation into cosmetic formulations (2). Other studies on the function of humectants also appeared since Griffin's treatise (229-231), with recent, more general reviews of their use discussed in such practical texts as DeNavarre's volume (232) on the manufacture of cosmetics.

Within the last two decades, many studies have been conducted to determine the mechanism of moisture-induced degradation of drug, pure and formulated. Leeson and Mattocks (233) investigated the stability of aspirin under varying conditions of RH and temperature. They concluded that solid state aspirin decomposition in the absence of moisture is negligible, but in its presence, rapid moisture adsorption occurs to an extent dependent on vapor pressure.

It is within this adsorbed film, whether submonolayer or multilayer, that drug rapidly dissolves to the extent of saturation and decomposes in solution. In their model it was assumed that the volume of adsorbed moisture was governed by the Freundlich isotherm.

The kinetics of p-aminosalicylic acid decomposition under varying RH's was studied by Carstensen and Pothisiri (234). To understand the role that adsorbed moisture played in the degradation of the solid compound, the authors measured moisture isotherms of the drug at several temperatures. Their conclusions were compatible with the sorbed moisture theory of Leeson and Mattocks (233). In an earlier study, Carstensen et al. (235) investigated the hydrolytic degradation of the water-soluble drug, thiamine hydrochloride, tabletted in a microcrystalline cellulose matrix of varying moisture content. Their results suggested that in the presence of sufficient moisture, the drug was adsorbed onto the excipient as a solution in which only the first layer was subject to decomposition. This behavior necessarily differs from that observed with the less soluble drugs in formulation.

The ultimate concern of those studying the mechanisms of moisture-induced drug degradation is to arrive at a means of controlling the phenomenon in the interest of long-term stability. Aspirin stabilization has been attained by dispersing it in a hydrophobic polymer such as dimethylpolysiloxane, thereby preventing the penetration of water to the intact drug during formulation storage (236). Attempts to correlate the effects of various excipients on aspirin stability with such bulk properties as porosity and tablet hardness have also been made (237,238). Similar studies of solid state stability have been conducted with ascorbic acid (237,239)and nitrazepam (240) as active ingredients. With only cursory attention to chemical stability, Scott et al. (241) attempted to correlate qualitatively the EMC's of formulation mixtures with those of the individual components. Using the "desiccator storage" method, they measured the moisture uptake rate by a number of pure excipients as well as by various granulations and tablets. They suggested that the hypothetical adsorption isotherm for a "hygroscopic solid" would have the characteristics of a Type II (Brunauer classification (14)) isotherm, common to physical adsorption leading to multilayer formation.

Interestingly, Hüttenrauch (219) observed that the hygroscopicity of sucrose was increased on destroying the crystal structure, e.g. by grinding. According to his results, the "hygroscopic point" (inferred to be equivalent to CRH) of amorphous sucrose appeared at approximately 50% RH, whereas that of the highly crystalline material adsorbed little moisture below 70% RH. He claimed to have eliminated the effect of changing particle size and surface area in his determinations.

The physical stability of solid dosage forms or powders in general, as affected by moisture, has had a longer history of attention, perhaps because poor bulk properties are more unmistakably troublesome than a chemically degrading ingredient comprising only a small fraction of the total material. Many early studies concerned the caking tendency of fertilizer powders, whose components are primarily inorganic salts of reputedly high hygroscopicity. Such caking on moisture adsorption has been attributed to increased cohesion as well as crystals "knitting" in solution and effectively recrystallizing together within the adsorbed film of moisture (224). Strickland (242)gathered the first substantial set of moisture isotherm data on pharmaceutical powders, both drug and excipient. Using the method of desiccator storage, he studied adsorption and desorption profiles. The pronounced hysteresis that appeared in most of the curves was attributed to failure to attain equilibrium. Also reported is an extensive list of materials, mostly active agents, which neither gained nor lost moisture on exposure to extreme RH's. Initial screening tests suggested that procaine base had a CRH below which no moisture was adsorbed, but above which sorption was rapid and extensive. Using the more sensitive quartz spring adsorption apparatus, further study of its in vacuo adsorption revealed clear formation of a dihydrate with no apparent hysteresis on desorption. Rate studies at very high RH indicated zero-order reaction between the base and water on hydration.

The surface properties of solids that determine static and dynamic bulk behavior have been thoroughly reviewed by many workers (227,243). Chikazawa and Kanazawa and others (193, 198, 218) have published a series of articles relating the changes in surface properties occurring on adsorption to the caking tendency of such materials as ground NaCl and urea. Of particular interest is their review on the hygroscopicity of water-soluble alkali metal halide salts (189) in which they discussed surface interaction mechanisms of adsorption, proposing that formation of "hydrated ions" precedes solubilization on the crystal surface and eventual deliquescence.

Flow characteristics of a powder are particularly critical to the ease with which it can be handled during formulation. Neumann (244) has reviewed the effects of moisture on powder flow, emphasizing in particular the correlation between moisture content and angle of repose. Craik and Miller (245) studied the flow properties of starch, sucrose, and sodium chloride under humid conditions, and concluded that the detrimental effects of adsorbed moisture could be somewhat reduced by the addition of magnesium oxide. Shotton et al. have performed extensive tests on the effects of humidity and temperature on the EMC (179), cohesion (178) and compaction properties of powders (205). In an attempt to resolve the controversy of whether moisture remains "free" (physically adsorbed) on uptake by starch or "bound" (chemisorbed), the authors applied the Clapeyron equation to their data to yield heats of adsorption. These calculated quantities for the starches and alginic acid were low, reflecting weak bonding characteristic of physical adsorption. They also noted a linear relationship between the logarithm of the EMC's of these materials and the RH, with little dependence on temperature. By contrast the moisture contents of the carbohydrates capable of chemical hydration were more temperature-dependent, typical of chemisorption.

Because starch is so frequently used as a disintegrant, there has been longstanding interest in how disintegration is actually effected by its presence. Disintegration could occur via swelling or via capillary suction of water into the matrix (164,246-248). Porosity and related characteristics have proven to be very significant parameters in monitoring the relative contributions of these factors (164, 248,249). Lowenthal and others have reviewed thoroughly the history of this controversy of sorption mechanism

(250-253) but through their own studies of the problem, have arrived at no clear conclusion themselves regarding the matter.

Similar questions have arisen concerning the sorption mechanism of tablet excipients other than starch. Many attempts have been made to correlate the rate of and equilibrium uptake with such properties as shear and tensile strength (254,255), disintegration times (219), tablet hardness and bulk densities (256,257) and compaction behavior (205,257). Recently Coelho and Harnby (223,224) treated the moisture adsorption by insoluble nonporous powders in a theoretical manner. They based their arguments on the Brunauer-Emmett-Teller (BET) model of layered adsorption, as governed by the Kelvin and Laplace equations once liquid bridges form between two particles. Such bridges, they contended, will remain stable above a certain critical relative humidity, below which moisture is present only as adsorbed vapor. The form of the water so retained, whether liquid or vapor, is thus determined by this critical vapor pressure. Furthermore they proposed that the binding forces in each situation and the bulk properties they induce in the powder are continuous functions of the actual humidity. A similar model for desorption was proposed by El-Sabaawi and Pei (24) for porous, insoluble powders. They suggested that at high RH's, capillary evaporation governed desorption, whereas EMC's in terms of multilayer coverage could be predicted at low RH's. In their model they implied strong correspondence between "degree of hygroscopicity" and "porosity".

Many of the adsorption studies cited heretofore have relied on the static method of desiccator storage, a simple and sufficiently accurate method under the appropriate circumstances of materials, conditions and intention. For those studies requiring more sensitive, accurate in vacuo measurement, the McBain-Bakr spiral quartz spring, also gravimetric, has long been popular (258). Less frequently used are volumetric techniques, often satisfactory for measuring equilibrium adsorption isotherms. In the last decade, however, the commercial production of the electronic microbalance has revolutionized the range of gravimetric capabilities with respect to sensitivity, precision, simplicity of data collection, continuous recording, and the ease of monitoring the sample simultaneously by other surface analysis techniques. It would prove futile to attempt summarizing all the adsorption work relying on microgravimetry; suffice it to say that a large proportion of the references listed in Table I utilized such methods. A review by Cadenhead and Wagner (259) presents a thorough discussion of gravimetric instrumentation and its primary applications. Czanderna and Vasofsky's recent review (260) offers exhaustive coverage of the adsorption literature whose data was generated using microbalance techniques (including electronic beam, helical spring, and quartz oscillator types), and in addition discusses recent technological developments in the area. Furthermore, many texts present thorough discussions of general gravimetric methodology (8,12,261, 262) as well as other surface analysis techniques (5,263).

It would be presumptuous and superfluous to attempt adding to the vast coverage of literature represented by the above references. A point in conclusion worth stating, however, is that, given the relative merits of the experimental techniques available, the electronic microbalance provides the most direct, sensitive, accurate, and universally appropriate tool with continuous output for monitoring both equilibrium and kinetic adsorption behavior.

EXPERIMENTAL AND RESULTS

Materials

Anhydrous $CaSO_4$[1], fumed silica[2], choline chloride[3], choline bromide[3], choline iodide[3], and choline bitartrate[3] were all used as received unless stated otherwise. When a sample was "ground," a glass mortar and pestle were used. Whenever possible, manipulation of the more hygroscopic chloride and bromide salts was performed within a plastic inflatable glove bag[4] in which a sub-ambient RH of 25-30% could be maintained. Various physical properties of the choline halides were measured according to the following procedures, the results of which are listed in Table II.

Density: Approximate densities of the halides were measured by suspending them in pure or mixed solvents in which they were insoluble. Following suspension and brief (1-2 min) centrifugation, it was noted whether the crystals had risen or settled in the tube. In this manner the densities were "bracketed" to within ±0.04 g/cm^3. Among the

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[1] Drierite, indicating. W.A. Hammond Drierite Co.

[2] Grade M5 Cab-O-Sil. Cabot Corp.

[3] Sigma Chemical Co.

[4] Model X-27-27. Instruments for Research and Industry.

solvents used were cyclohexyl chloride, methylene chloride, chloroform, carbon tetrachloride and 1,1,2,2-tetrabromoethane.

Surface area: All three halides were examined microscopically[5] from dilute suspension in light mineral oil. Sizing was performed using a glass hemacytometer slide[6] in which a grid of known dimensions is etched. The surface-volume mean diameter, d_{SV}, was calculated for each salt on the basis of three independent slide preparations. From these values the corresponding geometric surface areas, A_{geom}, were also calculated.

The Fisher sub-sieve sizer[7] was also used to measure the true surface area, A_{true}, of choline iodide. The chloride and bromide salts were not examined with the sub-sieve sizer because (1) they are too hygroscopic to withstand the flow of relatively moist air necessary to the determination, and (2) these particular samples' particle sizes exceeded that measurable by the instrument without modification.

Solubility: The salts were loaded into vials to which several drops of distilled water were then added. The vials

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[5] Instrument Division, Nikon.

[6] Spencer Bright-Line hemacytometer. American Optical Corp., Scientific Instrument Division.

[7] Fisher Scientific Co., Instrument Division.

were then closed and equilibrated at 25°C for several hours during which they were frequently agitated ultrasonically. Approximately 1 ml of supernatant was withdrawn from each vial and transferred to a second tared vial which was then rapidly closed and reweighed. With loosened caps, the vials were subjected to oven-drying at 120°C for 1 hr followed by vacuum-drying at 0.03 mm Hg/room temperature for approximately four hours. On withdrawal from vacuum, the vials were again rapidly closed and reweighed. From these data approximate solubilities could be calculated assuming all free water was removed during drying.

TABLE II. PHYSICAL PROPERTIES OF THE CHOLINE HALIDES*

		Cl	Br	I
Molecular weight		139.6	184.1	231.1
Density (g/cm^3)		1.20	1.52	1.78
Microscope:	d_{SV} (μ)	380.	174.	96.5
	A_{geom} (cm^2/g)	132.	230.	349.
Sub-sieve sizer:	d_{SV} (μ)	-	-	50.
	A_{true} (cm^2/g)	-	-	670.
Solubility (g/ml)		6.36	5.83	3.63
Molar solubility		∿46.	∿32.	∿16.

*Chloride and bromide samples oven-dried prior to testing.

Mercury used for the diffusion pump, mercury manometer and McLeod gauge was periodically cleaned according to the following procedure:

1. Withdraw amount to be cleaned via glass siphon from below the surface of the uncleaned mercury. (Regardless of the initial state of cleanliness, the mercury appeared clean following this simple procedure.)
2. Dropwise from a funnel fitted with a drawn pipet tip (so as to minimize drop size, maximize surface area), pass the mercury through a 50-ml buret filled with about 0.5 N HNO_3 (aq). Repeat at least once.
3. In a similar manner pass the mercury through fresh triply distilled water. Repeat at least once.
4. To rid the mercury of any retained moisture, place it in a shallow evaporating dish and heat to approximately 120°C on a hotplate for one hour under a hood with proper ventilation.
5. Store in an appropriate glass vessel after cooling to room temperature.

Initial Apparatus Design

Figure 1 shows a schematic drawing of the high vacuum manifold and microbalance apparatus at the completion of its initial stage of construction. All glass parts of the apparatus are Pyrex[8] fused by oxygen-gas torch. All valves are either vacuum stopcocks or hollow capillary stopcocks. The individual components are described below along with comments relevant to their use and performance on the apparatus.

Forepumps #1,2: Forepump #1[9] served as the primary pump for the vacuum manifold. Forepump #2[10] was used only to regulate the bulb pressure on the McLeod gauge via K. Both pumps were single stage gas ballast rotary high vacuum pumps capable of attaining approximately 0.1 mm Hg pressure within a short period of time.

Diffusion pump: The two-stage glass diffusion pump[11] was filled with mercury and driven by Forepump #1. The mercury in the reservoir was heated to boiling by a flask

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[8] Corning Brand borosilicate glass. Corning Glass Works.

[9] Cenco Hyvac 7. Central Scientific Co.

[10] Model ES35 "Speedivac". Edwards High Vacuum Ltd.

[11] Eck and Krebs Scientific Laboratory Glass Apparatus Co.

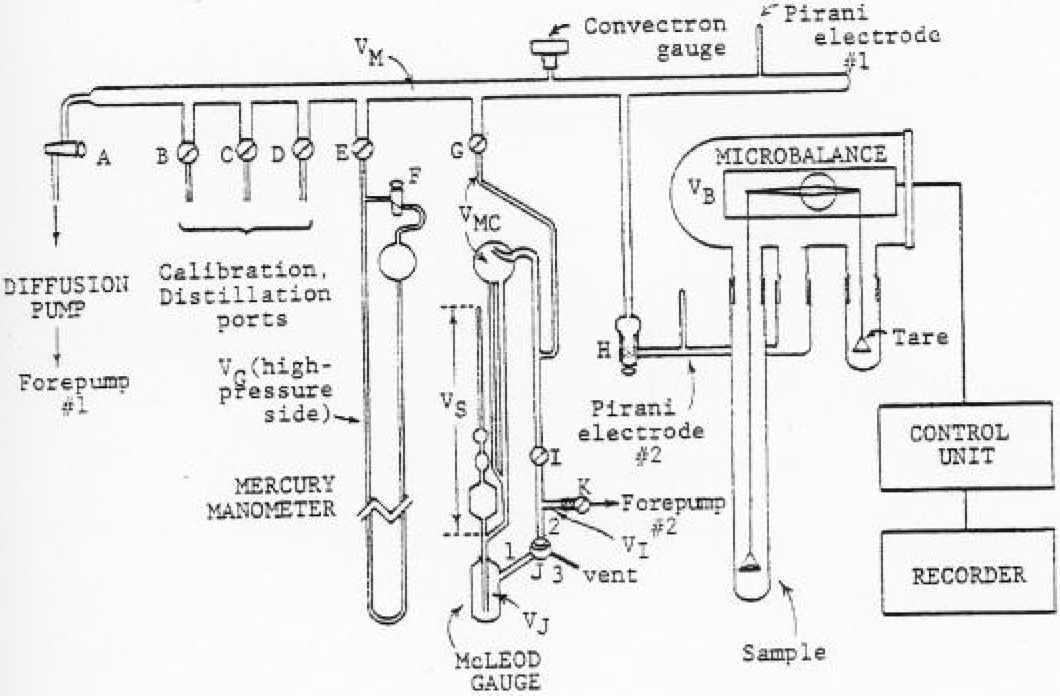

Figure 1. Adsorption apparatus at completion of initial stage of construction.

heater[12] (a nickel-chromium coil mounted in porcelain refractory with a cement asbestos radiation shield) controlled in temperature by a transformer[13] set at "100". An asbestos cover was wet-formed and dried around the reservoir and the entire tube containing the vaporized mercury. Cool tap water was run through the condenser jacket at a flow of about one liter per minute. Set up in this manner, the diffusion pump was capable of maintaining a vacuum of approximately 10^{-4} mm Hg on this apparatus.

Cathetometer[14]: Designed to measure vertical distances precisely, the cathetometer consisted of a laboratory telescope mounted on a vertical stainless steel rod 30 mm in diameter and long enough to permit the telescope to be moved through a vertical range of 100 cm. It was equipped with a 20-division vernier by which the position of the telescope could be read to the nearest 0.05 mm. Periodic calibration was necessary, normally needed when the tangent screw for the ocular required gross adjustment. Ideally, none should be necessary; even when properly calibrated, however, a ±50° adjustment of the tangent screw prior to each reading was not uncommon. The ocular focus needed little attention

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[12] Model HA-1. GCA/Precision Scientific Co.

[13] Powerstat. The Superior Electric Co.

[14] No. S-14785. Sargent-Welch Scientific Co.

as the manometer's arms were rotated such that the horizontal distance to levels measured remained essentially constant at about 3 m. Cathetometer measurements of a 300-mm long ruled scale placed at the same distance revealed good accuracy and precision: triplicate readings of the vertical scale length yielded an average value of 299.97 ± 0.29 mm.

Mercury Manometer: This was constructed with 6-mm i.d. tubing according to simple U-tube design; measurements of Hg levels were taken with the cathetometer. The height differential so measured is denoted P_{man} (in mm Hg).

McLeod Gauge[15]: The pre-calibrated McLeod gauge could measure pressures up to 25 mm Hg at three levels of sensitivity: 0-0.5, 0.5-5 and 5-25 mm Hg. It was capable of precise, discontinuous pressure measurements down to 1×10^{-4} mm Hg, unless condensable vapors were present, in which case the pressure read underestimated the true pressure (since such a vapor condensed under compression in volume V_s during the measurement). This rendered the gauge inaccurate for the measurement of water vapor pressure. (For example, with P_{man} registering 19 mm Hg water vapor pressure in an otherwise evacuated system, the McLeod gauge registered a value of

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[15] Todd Scientific Co.

0.9 mm Hg). Pressure measurements taken with this gauge will be denoted P_{mc} (in mm Hg).

Pirani Gauge[16]: Two Pyrex glass electrodes were fused onto the system so that the pressure within different regions of the manifold could be simultaneously monitored. The Pirani-type gauge required recalibration in the presence of water vapor. Availability of the control unit for these gauges rendered their use intermittent, however, and therefore they were used only as a "back-up" gauges. Pressure readings so taken are denoted P_{p1} or P_{p2} (in mm Hg) depending on which electrode was being monitored (see Fig. 1).

"Convectron" Gauge[17]: This metal gauge (with gauge tube port oriented vertically downward) was mounted via a metal-glass union[18] onto a 1/2-inch o.d. glass stub on the manifold. Leakage was prevented by lightly greasing the two O-rings in the fitting with Apiezon N stopcock grease[19]. Since this gauge also operated on the Pirani principle, recalibration was required for the measurement of water

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[16] Cat. No. 3596. LKB Instruments, Inc.

[17] Series 275 Convectron gauge. Granville-Phillips Co.

[18] Ultra-Torr fitting, Part No. SS-8-UT-6. Cajon Co.

[19] Apiezon Products Ltd.

vapor pressure. Pressure readings taken with this gauge are denoted P_{GP} (in mm Hg).

> NOTE: This gauge has an extremely sensitive filament which cannot withstand the high frequencies generated by a Tesla coil. If a Tesla coil must be used to test for manifold leakage, the gauge must be removed from the laboratory and replaced by a closed glass end via the same fitting.

Limited in accuracy and precision only by that of the cathetometer the P_{man} readings for both "dry" (water vapor pressure about zero) and "wet" (partial pressure of air about zero) atmospheres were taken as "true" pressures. Therefore calibration of the other pressure gauges was performed as functions of P_{man}. Calibration sensitivity suffered most, obviously, at very low pressures where the relative error associated with P_{man} measurement was large. The calibration plots so obtained are shown in Fig. 2.

Electrobalance[20]: The electrobalance, mounted inside a vacuum bottle, is designed to operate in high vacuum or in any controlled atmosphere. The microbalance has a weight capacity of 1 g with a minimum full scale recorder range of 2×10^{-6} g. For the purposes of this work, it was necessary

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[20] Model RG-HV. Cahn Instruments, Division of Ventron Corp.

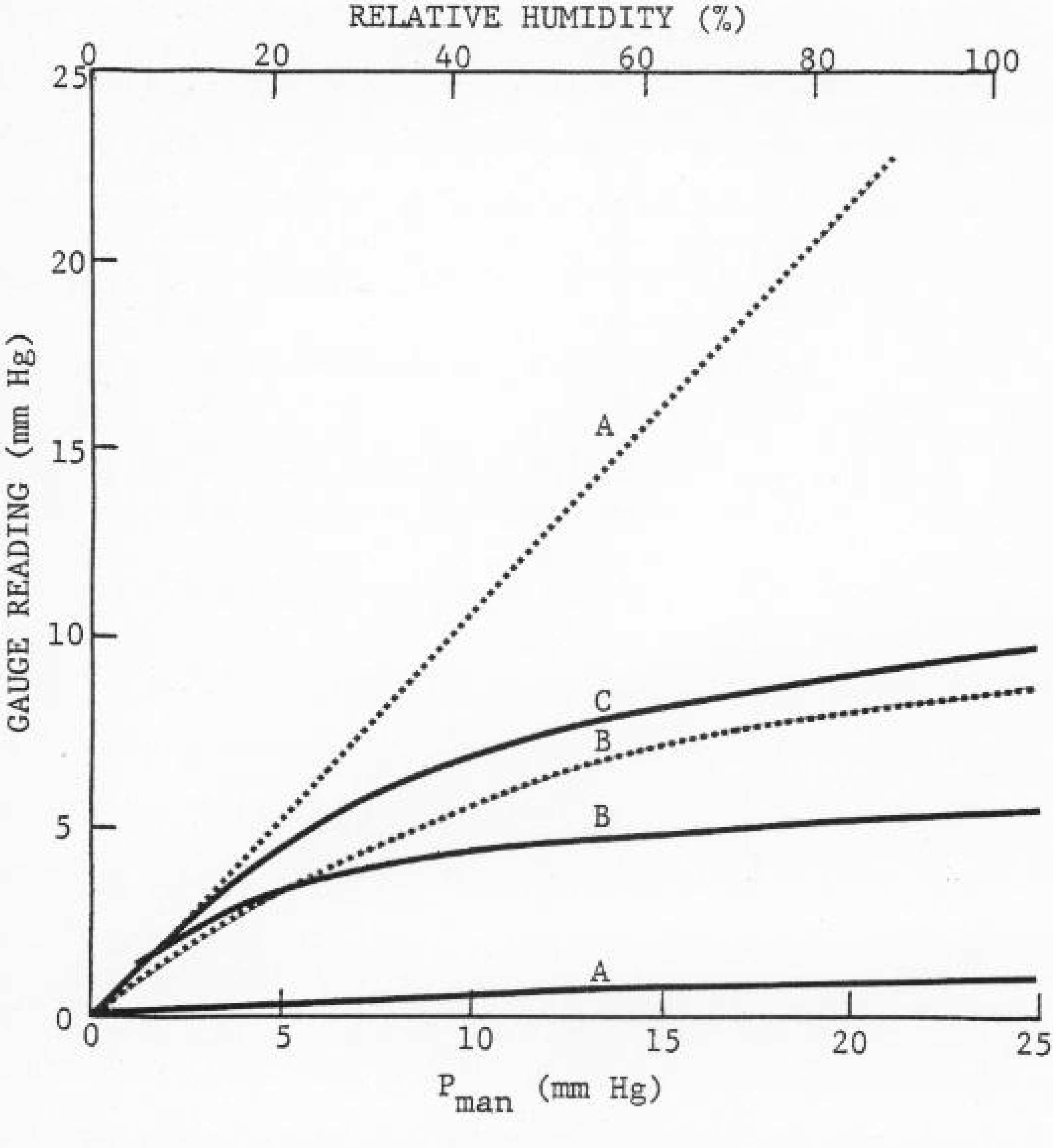

Figure 2. Pressure gauge calibration curves at 25°C.

KEY: ━━━ "wet" atmosphere
┈┈┈ "dry" atmosphere (RH scale not applicable)
A: P_{MC}; B: P_{GP}; C: P_{p2}

to be able to measure accurately weight changes on the order of 0.001 mg. For example, given a 50-mg sample of material characterized by a (relatively small) specific surface area of 10 m^2/g, the weight of moisture adsorbed per monolayer can be calculated (assuming a surface of 10.6 A^2/molecule H_2O):

$$10\ m^2/g = 0.5\ m^2/50\ mg = 0.5\cdot 10^{20}\ A^2/50\ mg.$$

Then

$$\frac{(0.5 \times 10^{20}\ A^2/50\ mg)(18\ g/mole\ H_2O)}{(10.6\ A^2/mol\ H_2O)(6 \times 10^{23}\ mols/mole)} = 1.4 \times 10^{-4}\ g$$

$$= 0.14\ mg\ H_2O \text{ per 50-mg sample.}$$

The large O-ring seal on the aluminum end cap of the vacuum bottle proved to be a primary source of leakage on the manifold. Periodic cleaning and light greasing with Apiezon N grease minimized this problem. The vacuum take-off tube was sealed with grease, without the provided O-ring, in the same manner as any other ground glass joint. Both the sample hangdown tube under pan "A" and the tare weight hangdown tube under pan "C" were sealed only by lightly greasing the O-ring supplied for each, since these tubes required frequent removal. These two joints and the end cap limited the extent to which high vacuum could be maintained.

NOTE: (1) The Tesla coil must be operated with caution in the vicinity of the microbalance. It is suggested by the instrument instruction manual that for the instrument's protection diode D-4 (normally on the weighing mechanism) be relocated to the control unit. Unplugging the balance from the control unit <u>at the bottle end cap</u>, leaving the weighing mechanism ungrounded, however, was also considered sufficient as a means of protecting the instrument[21].

<u>Recorder[22]:</u> A potentiometric recorder with variable span (adjusted to 1 mV) was connected to the electrobalance control unit for continuous weight recording.

Constant attention to the vacuum-holding integrity of the apparatus was required. As previously indicated, volume V_B (balance region) proved to be the primary source of leakage. To monitor leakage and to predict its effect on measurements over the course of time, a leakage rate (LR) was defined in units of liters per minute (lpm). Supposing that Δn moles air of molar volume $\overline{V}$ (at 298°K/760 mm Hg) under ideal behavior, leak into volume V over time course Δt, let

$$LR = \frac{\Delta n\overline{V}}{\Delta t} = \frac{\frac{\Delta PV}{RT}\,\overline{V}}{\Delta t} = \frac{\frac{\Delta PV}{RT}\;\frac{RT}{(760\ \text{mm Hg})}}{\Delta t} = \frac{\Delta P\cdot V}{760\cdot\Delta t} \qquad \text{Eq.(5)}$$

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[21] Personal communication, Cahn Instruments technical representative.

[22] Sargent.

where V = volume of region (1)

ΔP = change in pressure within V (mm Hg)

Δt = time elapsed (min).

Low leakage rates could be tolerated for particular measurements such as volume calibrations, especially if they plateaued with time. Furthermore, noting the pattern of vacuum loss served to distinguish between true apparatus leakage and vapor desorption from the walls of the apparatus. The latter, an equilibrium phenomenon, was typified by a plateauing LR, and could be controlled by successive evacuations.

Volume Calibration: It was desirable to determine the volumes of different regions of the apparatus. First, the volume of a 1-l round-bottom flask with ground glass neck was measured in triplicate by weighing before and after filling (to the bottom of the neck joint) with distilled water equilibrated to 24°C. Having measured the density of the undegassed water independently at 24°C (0.9958 g/ml), the volume of the flask was calculated to be 1061.8 ± 0.6 ml. Prior to fusion onto the manifold, port D was similarly calibrated in triplicate using mercury. With the stopcock closed, the joint was inverted and filled completely with mercury (with a reported density of

13.5413 g/ml (264)) equilibrated to 22°C. This volume of mercury was then weighed and calculated to represent a volume of 16.85 ± 0.05 ml. Summing the volume of the flask and port D yields the only directly measured volume on the apparatus, $V_c = 1078.6 \pm 0.6$ ml. Other volumes of the manifold were then measured by air expansion from V_c. To insure the air was dry (for accurate pressure measurement and to minimize adsorption effects), a drying tube (in series with a cold trap and a heating chamber containing copper windings) was secured to port B through which vacuum in the manifold could be released.

Volume calibrations were repeatedly performed in various combinations of successive expansion , to check internal consistency of the results. A typical expansion procedure and the resulting volume calculation (refer to Fig. 1 for "V" definitions) are outlined in Table III. The equations resulting from the pressure measurements following each expansion step are based on the simple relation:

$$(PV)_{initial} = (PV)_{final} \qquad \text{Eq.(6)}$$

These equations are numbered in association with the step in which they were generated.

$$740.00V_c + 0.001(V_M + V_G) = 425.70\{V_C + (V_M + V_G) + \Delta V_G\} \qquad \text{Eq.(III-3)}$$

TABLE III. VOLUME CALIBRATION (T_{lab} constant)

STEP	OPERATION	PURPOSE	P_{MC}	P_{man}	h
1	Open B,D,E. (A, C,G,H closed)	Measure atmospheric pressure P_{atm}; contain P_{atm} in V_c.	-	740.00	-
2	Close B,D; open A,E,H, then G.	Evacuate entire system except V_c.	0.0010	-	-
3	Close A,G,H. Open D.	Expand P_{atm} in V_c into evacuated $V_M + V_G$, causing increase in Hg manometer volume to $V_G + \Delta V_G$.	-	425.70	212.85
4	Open H.	Expand from V_c, V_M and $V_G + \Delta V_G$ into V_B $(+\Delta V_G')$.	-	134.60	67.30
5	Open G*.	Expand into $V_{MC} + V_S$ (McLeod gauge).	-	130.30	65.15

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*Caution must be exercised in expanding pressures in excess of 25 mm Hg into the McLeod gauge: the expanding atmosphere in the manifold must be slowly "dosed" via valve G, at the same time P_{atm} is similarly "dosed" via valve J to counter the rising pressure on the Hg reservoir from $V_{MC} + V_S$ and prevent "bumping".

where ΔV_G = A'h (units of ml) = increase in volume in high-pressure arm of manometer caused by introduction of vapor into the evacuated manometer

A' = cross-sectional area of manometer tubing = 0.02827 ($10 \cdot cm^2$)

and h = height of volume ΔV_G in column (mm).

Note that while h is calculable directly from the cathetometer readings, it is effectively equal to one half the newly established P_{man} reading. It is clear that the second term on the left-hand side of Eq. (II-3) is negligible with respect to the first term. It is also evident that as long as the expansion is successive, i.e. no volume is closed off once opened, that each step's $(PV)_{final}$ can be equated to the first expansion step's $(PV)_{initial}$. Thus Eq. (III-4) can be written:

$$740.00\ V_c = 134.60\ \{V_C + (V_M + V_G) + \Delta V'_G + V_B\} \qquad \text{Eq.(III-4)}$$

Likewise:

$$740.00\ V_c = 130.30\ \{V_c + (V_M + V_G) + \Delta V''_G + V_B + (V_{MC} + V_S)\} \qquad \text{Eq.(III-5)}$$

These equations can then be solved sequentially, knowing the originally determined calibration volume, V_c = 1079 ml:

$$740.00\ (1079) = 425.70\ \{1079 + (V_M + V_G) + 0.02827\ (212.85)\} \quad \text{Eq.(III-3)}$$

$$V_M + V_G = 790.6 \text{ ml}$$

$$740.00\ (1079) = 134.60\ \{1079 + 790.6 + 0.02827\ (67.30) + V_B\} \quad \text{Eq.(III-4)}$$

$$V_B = 4060 \text{ ml}$$

$$740.00\ (1079) = 130.30\ \{1079 + 790.6 + 0.02827\ (65.15) + 4060 + (V_{MC} + V_S)\} \quad \text{Eq.(III-5)}$$

$$V_M + V_S = 196.4 \text{ ml.}$$

Calculation directly from the geometry of the McLeod gauge yielded a value of $V_S = 42.02$ ml, therefore $V_{MC} = 154.4$ ml. The volumes V_M and V_G were separated in an expansion procedure wherein P_{atm} in V_c was expanded into $V_M + V_G$ $(+ \Delta V_G)$; P_{atm} was readmitted into V_c and V_M only, then V_M was re-evacuated; final expansion from V_c into $V_M + V_G$ $(+ \Delta V_G{}')$ yielded a set of simultaneous equations which could resolve the two volumes. Table IV summarizes the results of the volume measurements.

TABLE IV. VOLUMES (See Fig. 1)

V_c = 1079 ml	V_B = 4060 ml
V_M = 764 ml	V_{MC} = 154 ml
V_G = 27 ml	V_S = 42 ml

The reproducibility of these determinations was generally within ±2% and was often better, except for V_B in which apparent leakage depressed the value as much as 10%.

Preliminary Adsorption Experiments

Samples of calcium sulfate, fumed silica, choline chloride and choline bitartrate were subjected to adsorption or cycled adsorption/desorption runs on the apparatus as described above. A distillation flask containing about 10 ml triply distilled water was connected to port D to serve as a source of water vapor. This flask was evacuated to P_{GP} = 0.050 mm Hg by first freezing the water in a dry ice/methanol slurry, then evacuating the manifold with D open. Such degassing was repeated twice. The microbalance was calibrated according to Manual instructions to a full recorder range sensitivity of 1 mg. The sample of $CaSO_4$ was ground to a powder just prior to placement on the 25-mm aluminum sample pan on pan "A". For the silica and choline chloride runs, the samples were placed on the pan with no pretreatment. In each case the manifold including V_B were evacuated prior to the run until the sample weight was constant. Buoyancy corrections were not considered necessary at this time. Settings on the microbalance were:

Mass dial range (MDR) = 10 mg
Substitution weight (SUBST) = 50 mg
Recorder range (RR) = 10 mg (was changed during the run as necessary to keep signal on scale).

Initial sample weights were approximately 50 mg. Prior to "zero time", the flask containing water at port D was brought to room temperature, and with H closed, D was opened to allow water vapor to expand and equilibrate into the main manifold, excluding the McLeod gauge and V_B. The resulting water vapor pressure could be measured via either P_{man} (accurate for pressures above 3 mm Hg) or P_{GP} (insensitive for pressures above 3 mm Hg). Valve D was then again closed. At "zero time" adsorption was initiated by opening H, thereby expanding the water vapor in $V_M + V_G$ into the sample region V_B. This represented an expansion ratio (ER) of approximately 6.1 where, in general,

$$ER = \frac{V_{final}}{V_{initial}} \qquad \text{Eq.(7)}$$

and in this case

$$ER = \frac{V_M + V_G + V_B}{V_M + V_G} = 6.1$$

Therefore for an initial vapor pressure in the manifold of 23.756 mm Hg or 100% RH at 25.0°C (264), a vapor pressure of 23.756/6.1 = 3.89 mm Hg (16.4% RH) could be obtained in the sample chamber on expansion. (Using the calibration flask as additional ballast, an ER of 3.17 leading to a possible final RH of 32% could be obtained.) This could be further "dosed" via opening D, during the run, but the kinetics of uptake upon such dosing were quantitatively meaningless since a considerable lag time on evaporation, diffusion, and adsorption was incurred delaying the establishment of a new constant level of RH. Typical results of these runs are shown in Figs. 3, 4 and 5.

To gain some perspective for the sorption rates and equilibrium values that might be observed, choline chloride and choline bitartrate, described as "deliquescent crystals" and "hygroscopic on exposure to air" respectively (265), were each examined using the "desiccator storage" method mentioned earlier. Rather than desiccators, however, 750-ml wide-mouth, screw-cap amber bottles were used as chambers, five of which contained saturated salt solutions of LiCl, $CaCl_2$, $NaHSO_4$, $NaNO_2$ and NH_4Cl; a sixth chamber contained only distilled water for 100% RH. These salts were chosen from the list provided in Table V. Each sample was contained in a weighing bottle which had a wire handle wrapped around its neck for rapid withdrawal, capping and weighing at given time intervals. A beaker placed in each bottle provided a dry container for the sample during the run. Figures 6 and 7 show the uptake curves with time,

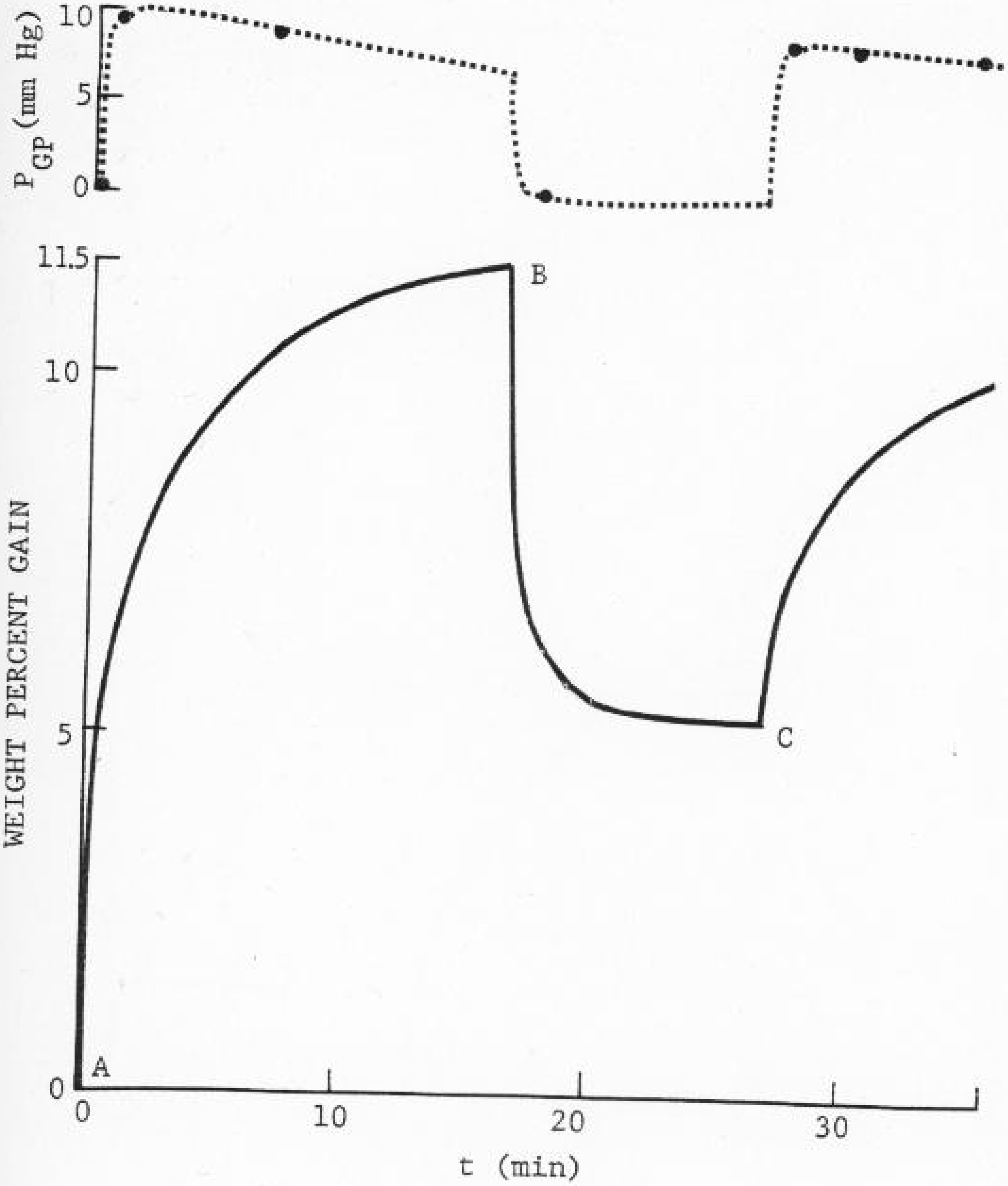

Figure 3. Adsorption of water vapor by $CaSO_4$ at room temperature. System "dosed" directly from 100% RH source for 5 sec at A and C, evacuated at B. Initial sample weight = 50.28 mg.

KEY: ——— Adsorption curve
········ Water vapor pressure profile (monitored by P_{GP})

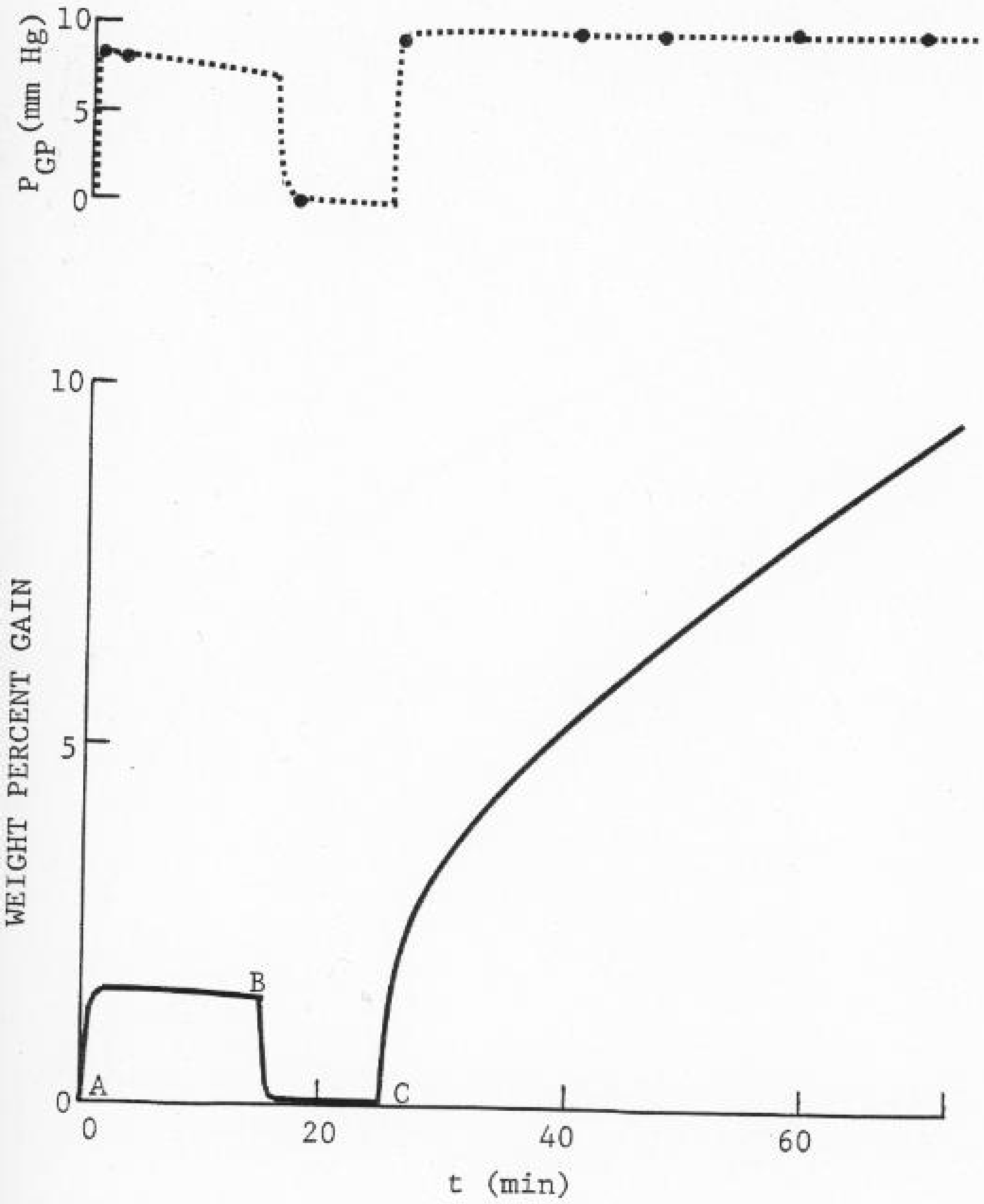

Figure 4. Adsorption of water vapor by fumed silica at room temperature. System "dosed" directly from 100% RH source for 5 sec at A, evacuated at B, re-exposed indefinitely to source at C. Initial sample weight = 50.52 mg.

KEY: ——— Adsorption curve
········ Water vapor pressure profile (monitored by P_{GP})

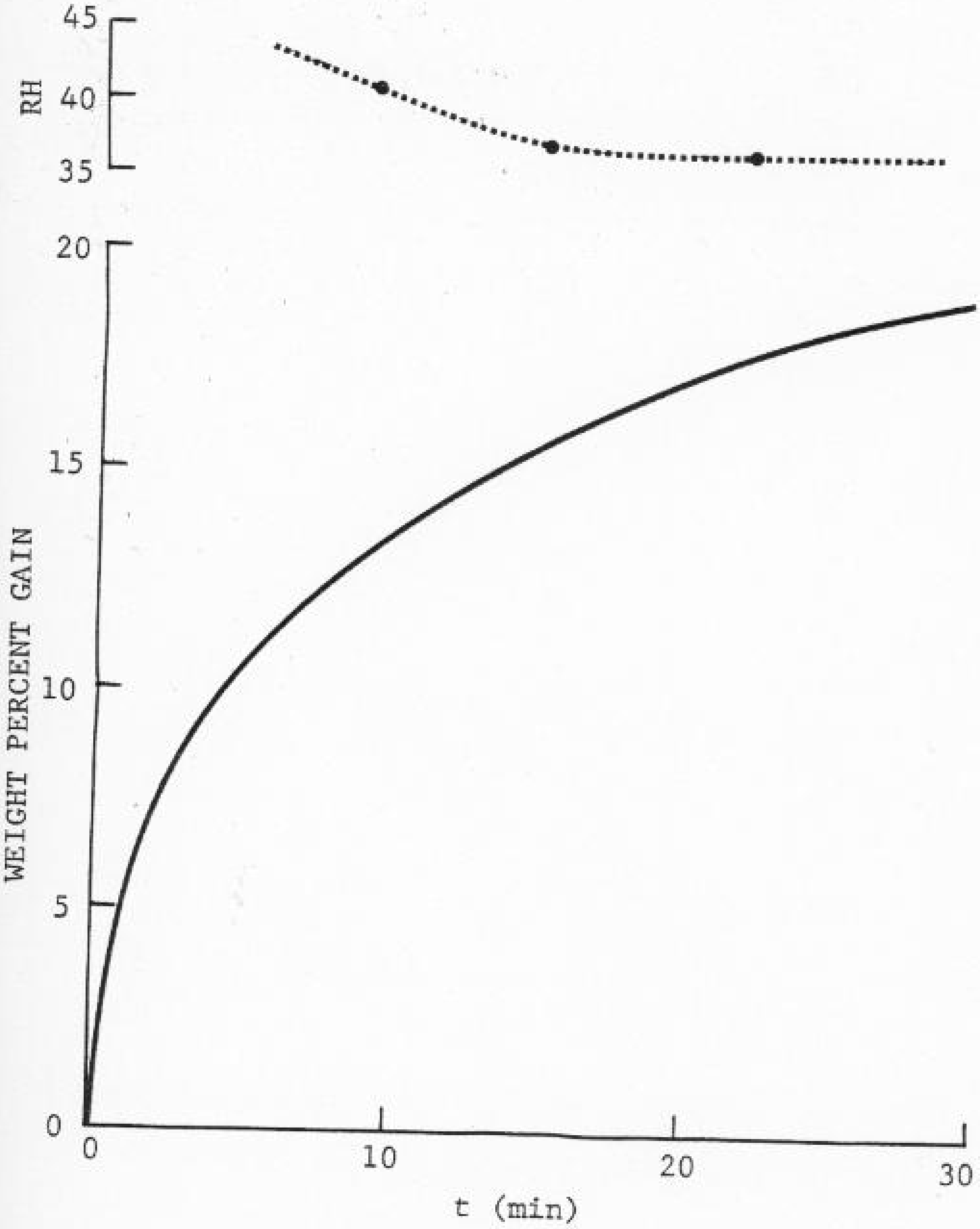

Figure 5. Adsorption of water vapor by choline chloride at room temperature. System "dosed" directly from chilled source for 5 sec at t = 0. Initial sample weight = 51.46 mg.

KEY: ▬▬ Adsorption curve
┈┈┈ RH profile (monitored by P_{man})

TABLE V. RH'S ABOVE SATURATED SALT SOLUTIONS*

	20°C	24.5°C	25°C
NaOH			7.03
LiCl	15		11.05
$KC_2H_3O_2$			22.45
$CaCl_2$	32	31	
KF			∿31
$MgCl_2$			33.00
NaI			38.5
K_2CO_3		43	42.76
$LiNO_3$			47.06
$Ca(NO_3)_2$		51	
$Mg(NO_3)_2$		52	52.86
$NaHSO_4$	52		
$Na_2Cr_2O_7$			∿55
NaBr			57.70
$NaNO_2$	66		64
Na_2CrO_4			66
KI			69
$SrCl_2$			70.83
$NaNO_3$			73.79
NaCl			75.28
NH_4Cl	79.5		79.3
KBr			80.71
$(NH_4)_2SO_4$			81.1
KCl			84.26
Na_2CO_3		87	
$BaCl_2$		88	90.19
KNO_3			92.48
$NH_4H_2PO_4$			93
$K_2Cr_2O_7$			98.00

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* These values were compiled from Refs. 4, 264, 266 and 267.

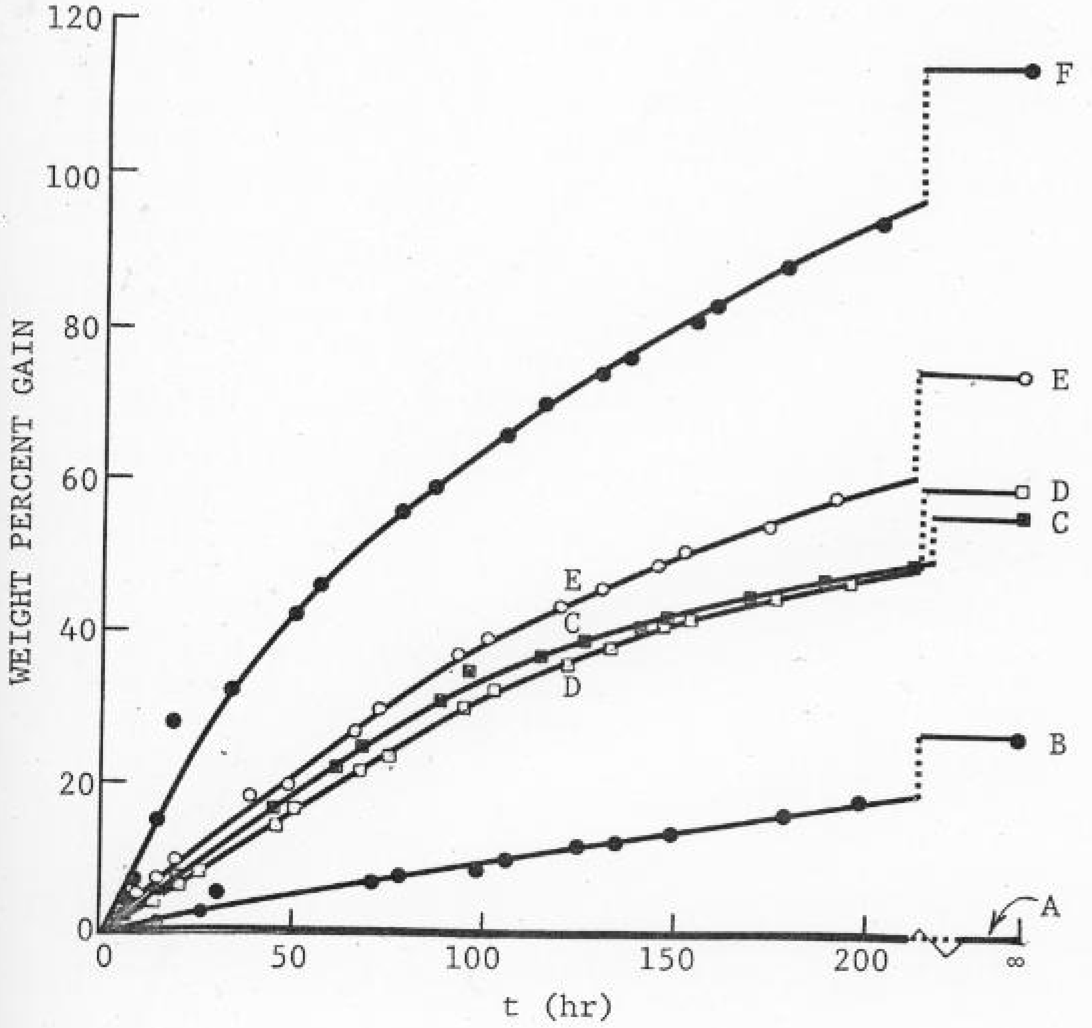

Figure 6. Adsorption of water vapor by choline chloride at room temperature using the desiccator storage method. Initial sample weights = 1.3-1.9 g.

<u>KEY</u>:
A: 12% RH
B: 31% RH
C: 52% RH
D: 64% RH
E: 79.5% RH
F: 100% RH

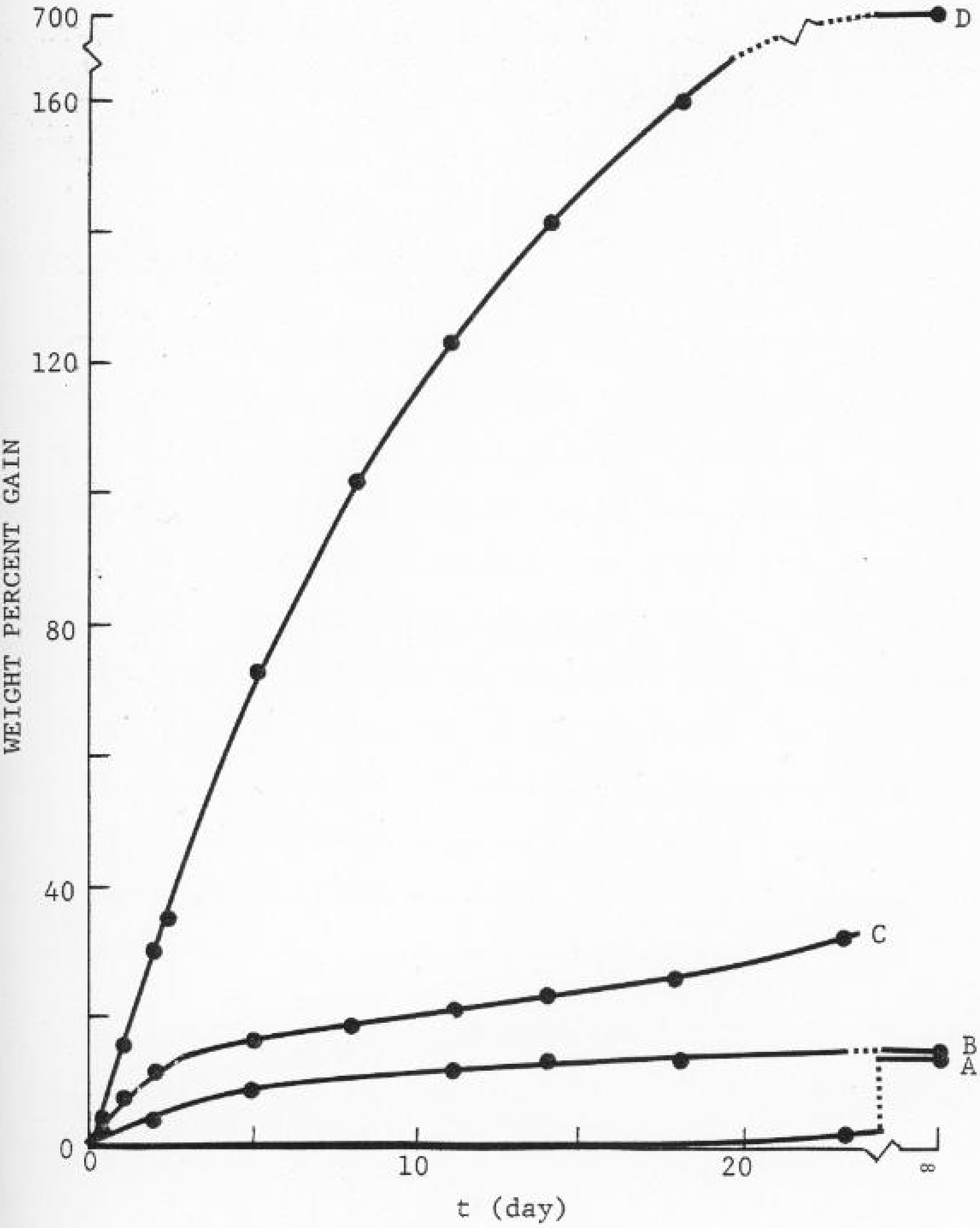

Figure 7. Adsorption of water vapor by choline bitartrate at room temperature using the desiccator storage method. Initial sample weights = 0.4-0.6 g.

KEY: A: 52% RH C: 79.5% RH
B: 64% RH D: 100% RH

while Fig. 8 is a plot of the equilibrium moisture uptake values at room temperature (uncontrolled, varying usually 21-24°C).

Modified Adsorption Apparatus

It is clear from the fluctuations in P_{GP} evident in Figs. 3, 4 and 5 that better control of RH was necessary to the collection of meaningful kinetic parameters. Lack of apparatus temperature control could have contributed to the variability of vapor pressure over longer time courses. Replacement of the water by a saturated salt solution in the distillation flask did not eliminate these fluctuations. These and other inadequacies of the apparatus (as shown in Fig. 1) and the experimental procedures that could be performed with it are summarized below; given in turn are the design modifications and additional equipment introduced to remedy these performance deficiencies.

(1) RH Stability. Clearly this is most important to kinetic studies, yet remains the most elusive property to control. The RH of the system should ideally remain absolutely constant from "zero time" to completion of the run, despite vapor depletion caused by adsorption to the inside walls of the apparatus or, more obviously, by rapid sample sorption. Furthermore, diffusion into the sample chamber

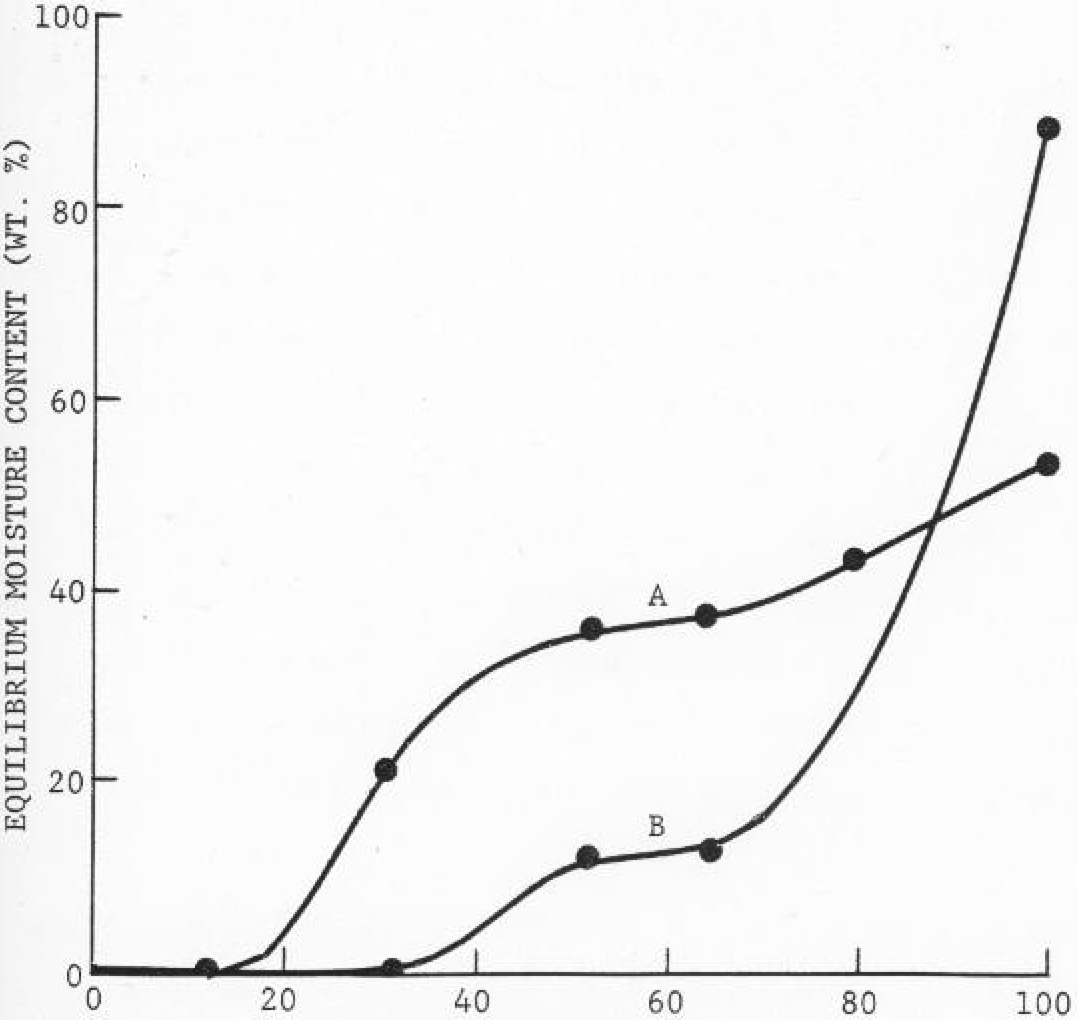

Figure 8. Equilibrium moisture content of choline chloride and choline bitartrate at room temperature as determined by desiccator storage method.

KEY: A: Choline chloride
B: Choline bitartrate

during expansion at "zero time" results in a finite lag in time to the final established RH; this cannot be avoided but it must be minimized.

Remedy: It was proposed that some type of "SUPPORT" RH chamber containing a saturated salt solution whose equilibrium vapor pressure equalled that of the desired final RH should be exposed to the sample immediately after expansion. In the interest of experimental versatility, seven such chambers on a separate isolatable manifold were attached to the main manifold as shown in Fig. 9. (Hereafter all "V" terms will designate components of the modified apparatus as identified in Fig. 9.) These chambers are denoted S1 through S7 in accordance with their stopcock identities. These same saturated solutions also served as "SOURCE" RH chambers for equilibration of the system (V_B excluded) to the initial RH prior to expansion.

Potential SOURCE:SUPPORT combinations demanded the equality of two ratios: (a) the ratio of the salt chambers' equilibrium RH's (initial:final) and (b) the ER of the expansion. The values of the former ratio are controlled by the selection of salts chosen for S1-S7. The values of ER are controlled by the various expansion schemes of which the apparatus is capable; these are listed in order of decreasing ER in Table VI along with Scheme identities.

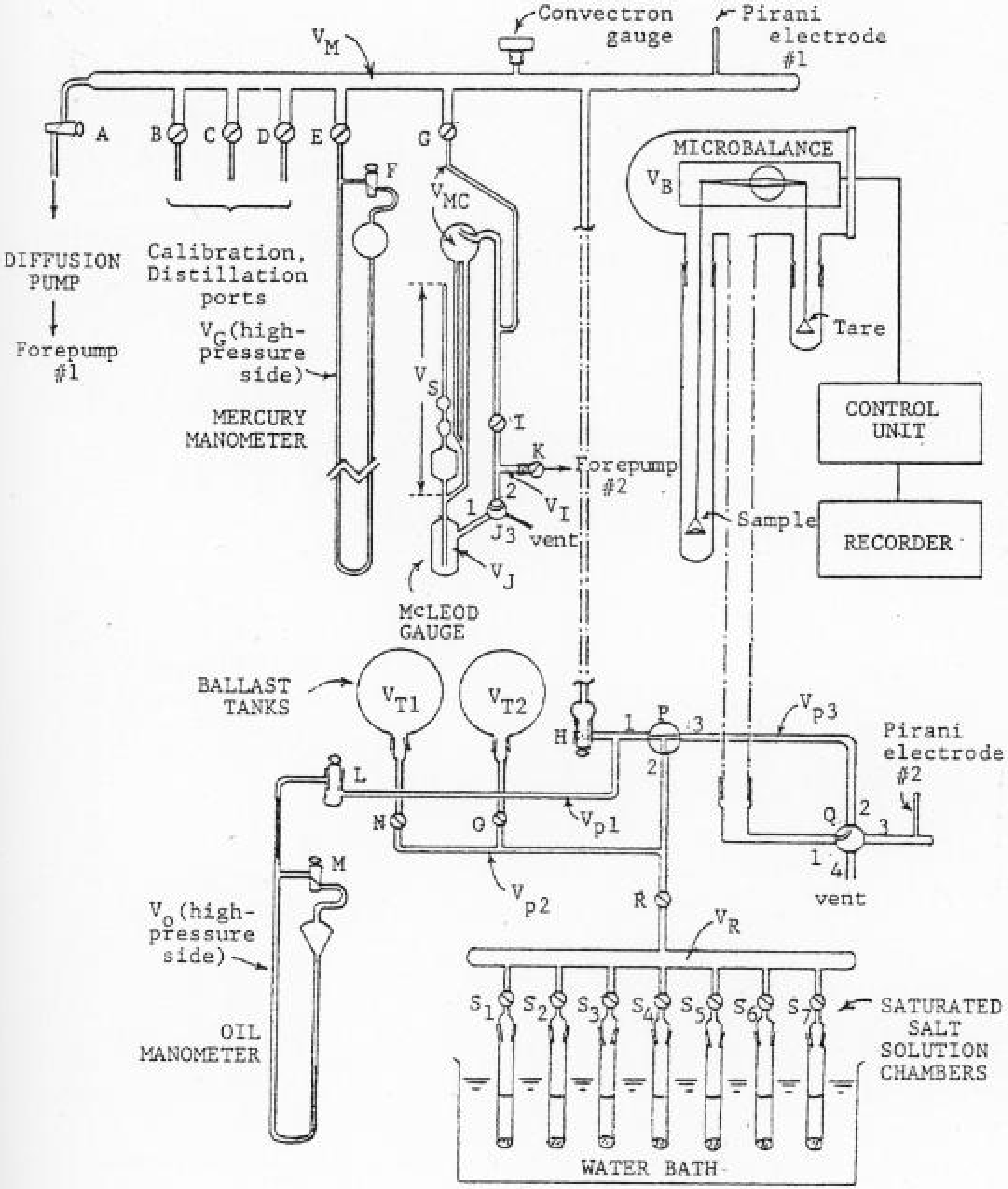

Figure 9. Modified adsorption apparatus.

TABLE VI. VOLUME EXPANSION COMBINATIONS*

EXPANSION SCHEME	ER	V_C	V_M	$V_{P1}+V_o+V_R+V_{P2}$	V_{T1}	V_{T2}	V_B+V_{P3}
A	18.	F	F	I	F	F	F
B	16.5		F	I	F	F	F
G	15.4			I	F	F	F
C	13.7	F	F	I	F		F
D	12.1		F	I	F		F
H	11.1			I	F		F
E	9.30	F	F	I			F
J	8.77	F	I	I	F	F	F
M	8.02		I	I	F	F	F
F	7.75		F	I			F
I	6.70			I			F
K	6.64	F	I	I	F		F
N	5.89		I	I	F		F
P	5.01	I	I	I	F	F	F
L	4.52	F	I	I			F
Q	3.80	I	I	I	F		F
O	3.76		I	I			F
BB	3.36	F	F	I	I	F	F
DD	3.07		F	I	I	F	F
FF	2.87			I	I	F	F
V	2.80	F	I	I	I	F	F
R	2.60	I	I	I			F
X	2.56		I	I	I	F	F
CC	2.54	F	F	I	I		F
S	2.30	I	I	I	I	F	F
EE	2.25		F	I	I		F
W	2.12	F	I	I	I		F
GG	2.06			I	I		F
Y	1.88		I	I	I		F
HH	1.85	F	F	I	I	I	F
T	1.71	I	I	I	I		F
II	1.69		F	I	I	I	F
Z	1.67	F	I	I	I	I	F
JJ	1.58.			I	I	I	F
AA	1.53		I	I	I	I	F
U	1.46	I	I	I	I	I	F

---

*I = Initial volume regions; F = Regions into which initial volume is expanded.

(Determination of the volumes on the modified apparatus will be discussed later.)

(2) RH Range. Following initial construction the apparatus was limited to providing a maximum 32% RH on expansion, a result of the large relative volume of the sample and balance chamber.

Remedy: The range of final RH's obtainable was increased in two ways: (a) maximizing the apparatus (excluding the sample chamber) volume by the addition of two large ballast tanks (V_{T1} and V_{T2}), and (b) minimizing volume V_B by placing the stopcock Q as close to the balance chamber as possible. A minimum ER of 1.46 was obtained in this manner. (Note: replacing the 1-l. calibration flask at point D (= V_c) with a 2-l. flask would yield a minimum ER of 1.41).

(3) RH Monitoring. As alluded to earlier, precision of the Hg manometer readings was poor below $P_{man} \sim 3$ mm Hg (deviations exceeding ±10%). While difficult to calibrate reliably against P_{man} at these lower pressures, the Convectron gauge (P_{GP}) provided at least a sensitive measure of vapor pressure. But at $P_{man} > 3$ mm Hg, P_{GP} values plateaued (in a "wet" atmosphere), limiting severely the device's range of sensitivity. A gauge sensitive and accurate over the entire range of 0-100% RH was needed.

Remedy: An oil manometer capable of registering vapor pressures up to ∿ 30 mm Hg (limited only by manometer height) was constructed and connected to the manifold via stopcock L. Because of its relativly low vapor pressure (listed as 1 x 10^{-4} mm Hg at 25°C), a standard grade vacuum pump oil[23] was selected for the manometer fluid. Its low specific gravity (listed as 0.89 g/ml at 25°C) rendered the new manometer 15.21 (= $\text{density}_{Hg}/\text{density}_{oil}$) times more sensitive than the Hg manometer. Thus at 10% RH/25°C, P_{man} = 23.756 (mm Hg) equalled an oil manometer pressure of P_{oil} = 362.10 (always expressed in units of mm oil). The cathetometer was used to take P_{oil} readings with oil levels read to the bottom of the meniscus. As the oil is practically transparent, accuracy and precision of these readings was greatly enhanced by taping a strip of white paper marked with a thin red vertical line to the back of the manometer arms, which, on diffraction through the oil, clearly defined the meniscus. (Mercury manometer readings were similarly clarified.)

Since the oil columns could easily cavitate with sudden changes in pressure, a section of capillary tubing (∿ 15 cm in length) was incorporated into the low-pressure arm to slow the fluid movement. This probably served

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[23] "Precision-B". GCA Corporation.

to over-correct the potential problem, however, and introduced a large lag time (1-2 min) in the response of the manometer to large pressure changes. (This is an intrinsic disadvantage to the use of oil anyway: since it wets the glass as opposed to mercury, its response will in any event be slower than that of mercury.) Thus to monitor "zero-time" RH attainment and stability, P_{GP} readings (which exhibited immediate response) were taken; the earliest stable P_{oil} measurement was then relied upon to establish an accurate value for the final RH. (Cathetometer measurements proved far too time-consuming for the frequent P_{oil} measurements required during the initial period of adsorption; it was found that attaching a carefully calibrated scale to the back of the manometer enabled accurate column height differentials to be read rapidly and directly.) This response lag could be practically eliminated, however, by "presetting" the manometer to the expected P_{oil} reading (corresponding to the final RH) prior to initiating the run. The calibration curve of P_{oil} vs. P_{man} is given in Fig. 10. The slope of the curve differs from the ideal slope of 15.21 by less than one percent, so that the ideal density ratio was used to convert P_{oil} to P_{man}. Therefore

$$\%\ \mathrm{RH} = \frac{P_{oil}}{(23.756)(15.21)}(100) = \frac{P_{oil}}{3.6133}\,. \qquad \text{Eq.(8)}$$

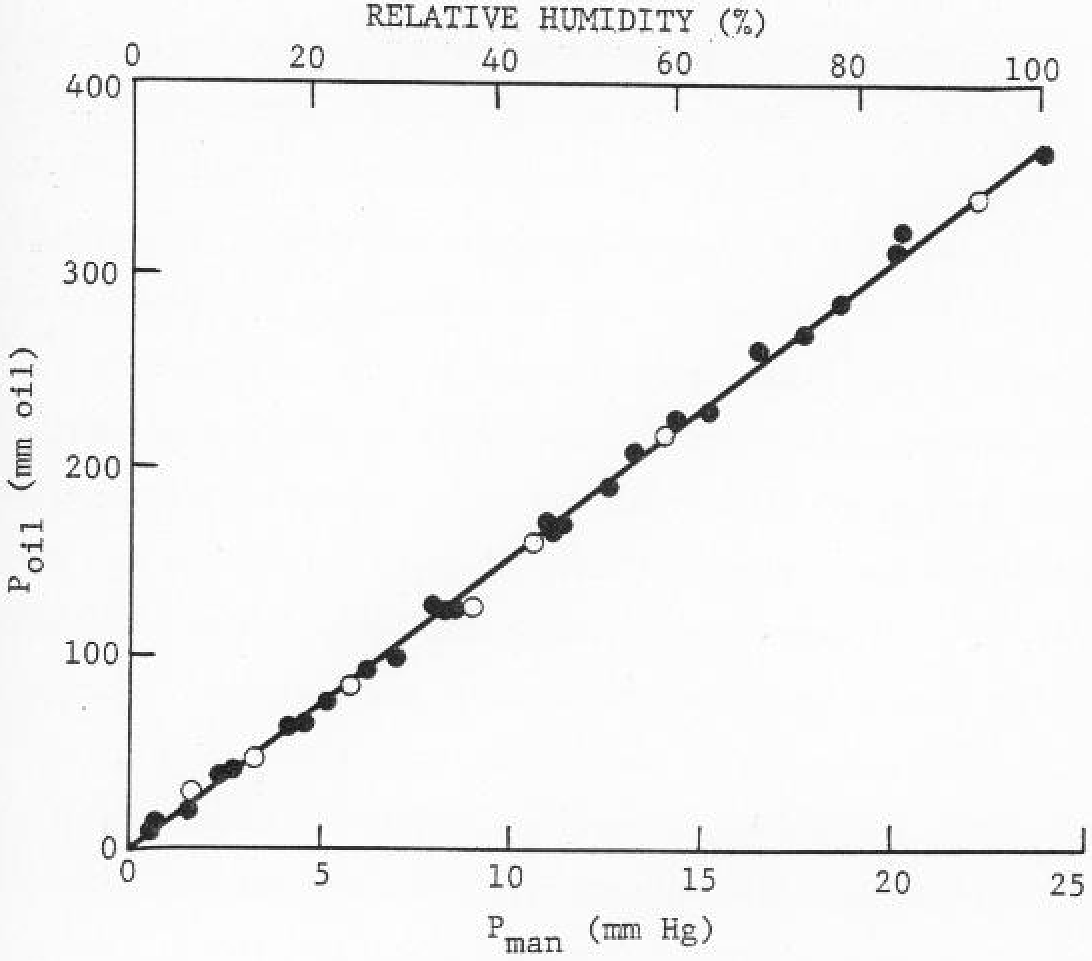

Figure 10. Oil manometer pressure calibration curve.

<u>KEY</u>: ● "Dry" atmosphere
○ "Wet" atmosphere

(4) Temperature Stability. While RH as controlled by saturated salt solutions is relatively insensitive to temperature, adsorption can be highly T-dependent. Furthermore, T gradients throughout the apparatus had to be minimized since the components' performance could be influenced by temperature fluctuations. For example, the value of $P_{oil}:P_{man}$ changes if the manometers are at different temperatures; or, if the pressure gauges, salt chambers and sample are all at different temperatures, the measured RH is in fact invalid. The heat given off by either forepump and especially that of the diffusion pump served to establish severe gradients within the system.

Remedy: Shields comprised of polyethylene sponge packing sheets 4 cm thick were sandwiched in aluminum foil and placed around the diffusion pump to insulate it from the manometers and salt chambers to the side and ballast tanks above. Blocks of the same material were packed loosely around the forepumps. A water bath maintained semi-manually at 25° ± 0.2°C containing an immersion heater[24] and circulating pump[25], was raised from below to immerse the entire rack of RH chambers S1-S7. Evaporation was minimized by placing a layer of styrofoam 4 cm thick on the water surface. Efflux from the pump was directed via

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[24] Automerse. Fisher Scientific Co.

[25] Easy-Whitewater Pump Co.

Tygon tubing to a water jacket that fit the sample hangdown tube to within ∿ 4 mm of its outside diameter; this gap was filled with a stagnant water layer. Efflux from the water jacket was returned to the water bath. Vibration from the pump, transmitted to the weighing mechanism through the rack support and causing undesirable noise in the recorder output, was damped almost entirely by mounting the pump on rubber feet within the water bath and supporting it independently by ringstand from the floor; polyethylene sponge wedged loosely between the water jacket and sample tube prevented any vibration transmission via their unintended contact.

(5) Sample Preparation: Initially no sample pretreatment was conducted, yet handling the more hygroscopic materials, e.g. choline chloride, revealed that deliquescence could occur within minutes under ambient laboratory conditions. It was clear that considerable "free water" could be picked up by samples simply during rapid loading into the chamber; not all of this water would be likely to desorb on room-temperature evacuation. Initial moisture contents required some means of standardization.

Remedy: It was proposed that each sample be subjected to a standard pre-run desiccation at elevated temperature *in vacuo*. For this purpose a crucible furnace[26] was used which

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[26] Type 56311. Lindberg, Division of Sola Basic Industries

could be elevated into position from below the sample tube (water jacket removed). The sample was thereby heated to $\sim 130^{o}C$ under continuous evacuation until its weight stabilized. It was supposed that such treatment would at least remove all "free" water. Removal of the heater and replacement of the water jacket brought the apparent sample temperature back to $25^{o}C$ within $\sim$ 1/2 hr; again, weight stabilization served as an indicator that the sample had equilibrated to room temperature. A shield comprised of asbestos mat sandwiched in aluminum foil was fitted to the weighing mechanism bottle to protect it from the furnace radiation; it also served to moderate any light fluctuations in the laboratory which could otherwise influence the photocell controlling the balance beam position.

Volume Calibration: Accurate volume calibration was necessary to accurate ER calculations. Volumes of the modified apparatus were calibrated by expansion from volume V_c in the same manner as described in Table III. (Of those volumes listed in Table IV only V_M and V_B should have changed on modification.) To measure the many component volumes in a single calibration, as many as eight expansion steps were necessary; it was deemed more accurate, however, to perform several one-, two-, or three-step expansions. Replication of various expansion combinations yielded the results given in Table VII:

TABLE VII. VOLUMES (see Fig. 9)

V_c = 1078.6 ± 0.6 ml*

V_M = 740.0 (± 0.6)

V_G = 21.1 (± 0.6)

V_{MC} = 154*

V_S = 42.02 ± 0.01*

V_o = 25.7 (± 0.7)

V_{P_1} = 45.3 (± 1.9)

V_{P_2} = 117.8 (± 1.1)

V_{P_3} = 32.3 (± 0.6)

V_R = 511.4 (± 1.6)

V_{T_1} = 3064 (± 10)

V_{T_2} = 3063 (± 13)

V_B = 3959 (± 9)

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*As previously determined.

Final Adsorption Experiments

Once the physical dimensions of the modified apparatus were fully determined and its components' performance verified, final adsorption experiments could be performed. First, however, an appropriate series of saturated salt solutions was chosen from Table V so as to optimize use of the RH chambers. These are discussed in the following section, along with a stepwise summary of the experimental procedure. Finally, the results of adsorption by several choline salts are given.

RH Chambers: Table VIII gives the selection of salts used for chambers S1-S7 as well as the corresponding ER's necessary for their combinations as SOURCE:SUPPORT pairs. Also listed is the approximate weight of salt required per 50 ml water to insure saturation at 25°C. Prior to use, each chamber was frozen carefully in dry ice/MeOH and evacuated to $P_{GP} < 3 \times 10^{-3}$ mm Hg; this was repeated at least twice to insure adequate degassing. (Note: (1) The insertion of 1/2-inch Teflon-coated stirrer bars for chamber solution agitation led to incomplete degassing: air entrapped within the stirrer bars continued to leach out over extended periods of time under vacuum. (2) Freezing the salt solutions too rapidly within the long narrow chambers led to tube breakage several times; this was alleviated by

TABLE VIII. SOURCE:SUPPORT PAIRS (25°C)

SOURCE				SUPPORT (SOURCE RH:SUPPORT RH Ratio[a])							
Salt	Chamber Identity	g/50 ml	RH[b]	S_6A	S_7A	S_2	S_3	S_4	S_5	S_6	S_7
KNO_3	S_1	25	92.48	1.10	1.25	1.60 (JJ)	2.16 (W)	2.80 (V,FF)	4.12	8.37	13.16
KCl[c]	S_6A	30	84.26	-	1.14	1.46 (U)	1.97	2.55 (CC,X,R)	3.75 (O,Q)	(7.62)[d] (F)	(11.98)[d] (D)
$NaNO_3$[c]	S_7A	50	73.79	-	-	1.28	1.72 (Z,II,T)	2.24 (EE,S)	3.29 (BB)	(6.68)[d] (K,I)	(10.50)[d]
NaBr	S_2	50	57.70	-	-	-	1.35	1.75 (T)	2.57 (CC,X,R)	5.22	8.21 (M)
K_2CO_3	S_3	70	42.76	-	-	-	-	1.30	1.90 (HH,Y)	3.87 (O,Q)	6.08 (N)
$MgCl_2$	S_4	125	33.00	-	-	-	-	-	1.47 (U)	2.99 (DD)	4.69
$KC_2H_3O_2$	S_5	200	22.45	-	-	-	-	-	-	2.03 (GG)	3.19
LiCl	S_6	80	11.05	-	-	-	-	-	-	-	1.57 (AA,JJ)
NaOH	S_7	40	7.03	-	-	-	-	-	-	-	-

[a] Appropriate Schemes with ER's within 3% of the RH ratio are given parenthetically.

[b] Ref. 268.

[c] KCl (S_6A) and $NaNO_3$ (S_7A) substituted for LiCl (S_6) and NaOH (S_7), respectively.

[d] These pairs not presently set up on manifold at same time.

minimizing the volume of saturated solution, freezing it slowly, and when repair was necessary, replacing the bottom of the cylindrical chamber with a round-bottomed bulb to allow freer expansion on solidification.)

Experimental Procedure: The following sequence of steps was generally followed in performing an adsorption run.

(1) Check electrobalance calibration (SET 5, SET 0/10) and recorder zero. Electrobalance settings: MDR = 100, SUBST = 20, RR = 10.

(2) Load sample (∿ 40 mg) onto pan "A" and fit hangdown tube into place.

(3) Evacuate system via A to $P_{GP} < 5 \times 10^{-3}$ mm Hg. (At least B, C, F, G, M closed; at least A, H, P_{13}, Q open, where for "P_{ij}", "ij" indicates the specific position of a multi-way stopcock as denoted in Fig. 9.)

(4) Raise crucible furnace until sample is well submerged into furnace region. Under continuous evacuation heat sample to ∿ 130°C; when sample weight stabilizes, lower furnace, remove, and fix water jacket in place around the sample hangdown tube.

(5) Turn P to P_{12} position, isolating balance from rest of system.

(6) Close A; with stopcocks set open/closed corresponding to the "initial volume" of the desired expansion

scheme (Table V), open the SOURCE RH chamber stopcock to equilibrate system to the initial RH (allow ∿ 1/2 hr).

(7) Preset P_{oil} to the desired final RH (i.e., RH at which adsorption run is to be conducted). Close L.

(8) Check that sample has returned to room temperature by verifying weight stabilization.

(9) Immediately prior to "zero time":
   a. Record P_{GP}.
   b. Start chart.
   c. Close SOURCE RH chamber stopcock.
   d. Open all stopcocks <u>except P</u> to "final volume" positions.

(10) At "zero time": Turn P_{12} to P_{123} for expansion into V_B.

(11) Immediately after "zero time":
   a. Open SUPPORT RH chamber stopcock.
   b. Open L.
   c. Monitor P_{GP} and P_{oil} throughout run.

(12) Monitor sample disposition for onset of deliquescence.

It should also be noted that unless $T_{lab} \gtrsim 25^{\circ}C$, condensation could occur to a lesser or greater extent within the system, eliminating control over the final RH.

According to the above procedure three choline halide salts were examined under varying RH's. Results of selected runs are shown in Figs. 11, 12 and 13. For these curves and their corresponding RH profiles, initial uptake rates (or initial slopes) were calculated, as taken from the earliest portion of the curve where the RH appeared to have stabilized. The approximate onset of observable deliquescence is noted on the curves with a star. The adsorption rates from several representative curves are plotted as a function of weight gain in Fig. 14. Linearization of the later adsorption curve could be obtained by plotting $\ln\{(W_\infty-W)/W_\infty\}$ vs. t, as done for several representative curves in Fig. 15. Initial rates of uptake expressed in weight percent gain per time (γ') are then plotted as a function of RH for each of the salts in Fig. 16.

Close inspection of Table VIII reveals that no SOURCE: SUPPORT pairs were available for obtaining a final RH of 92, 84, or 74%. Nevertheless data were successfully collected at these higher RH's without relying on the expansion/SUPPORT RH system otherwise used. It was determined that exposure of the sample chamber to the maximum RH less than that of the sample's characteristic RH_o would establish a significant partial vapor pressure of water within V_B as well as allow any adsorption to the walls of the apparatus to take place prior to "zero time" without affecting the sample. This largely eliminated the major causes of lag in obtaining a stable RH. Reasonably rapid attainment of the final RH could

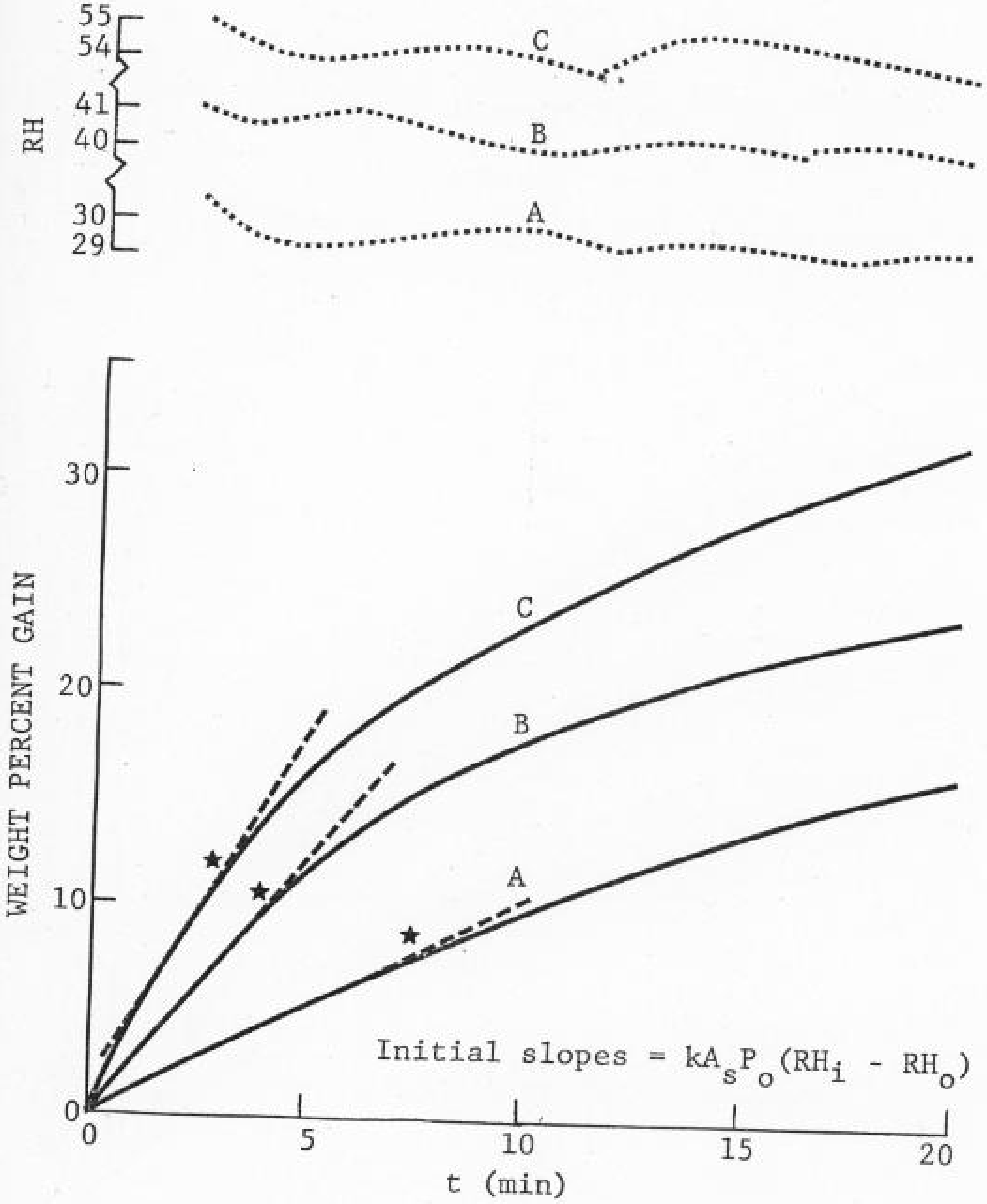

Figure 11. Selected curves illustrating the adsorption of water vapor by choline chloride at 25°C.

<u>KEY</u>: ——— Adsorption curve
·········· RH profile (from P_{GP} and P_{oil})
A: 29.5% RH
B: 40.5% RH
C: 54.5% RH
★ Onset of deliquescence

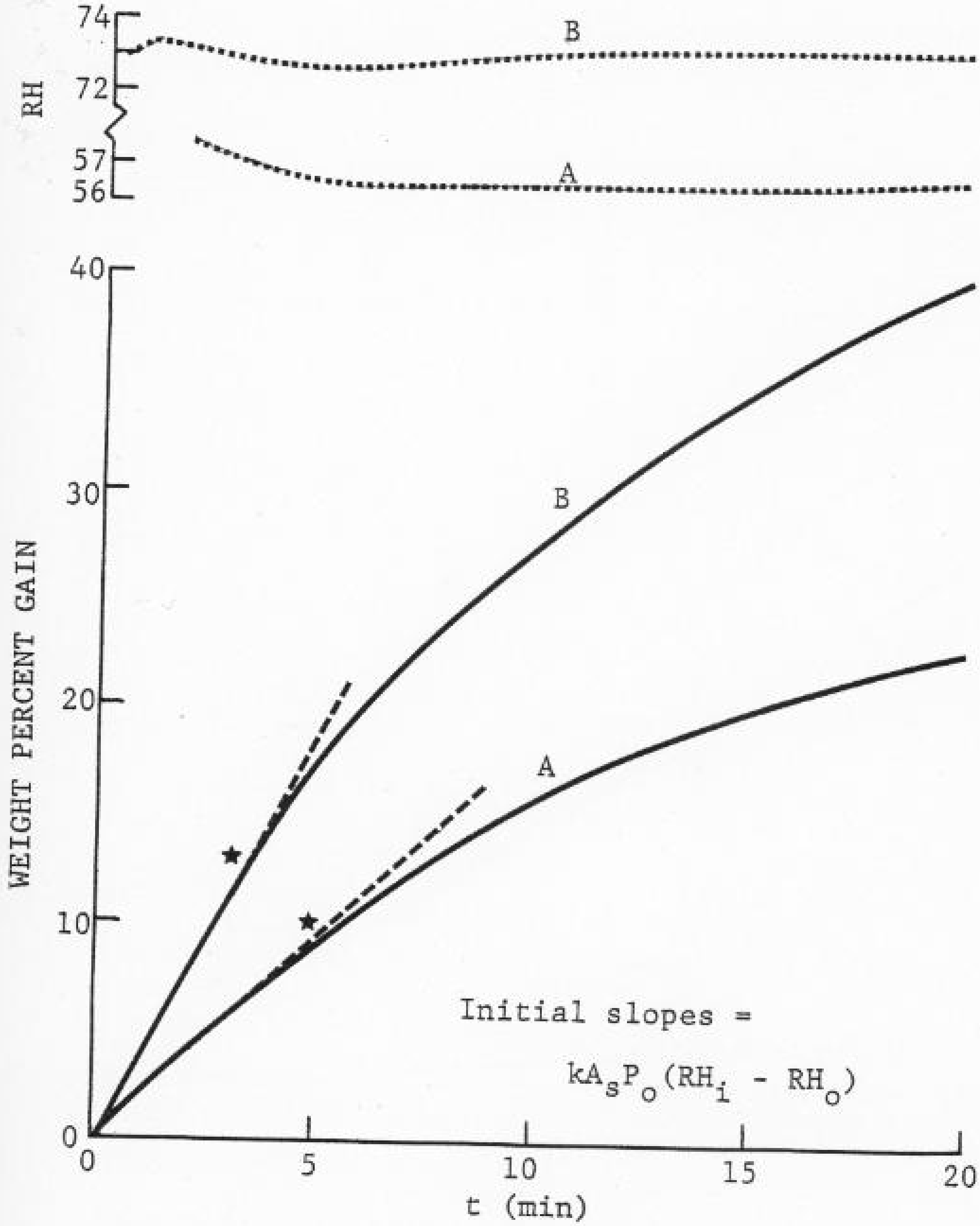

Figure 12. Selected curves illustrating the adsorption of water vapor by choline bromide at 25°C.

KEY: —— Adsorption curve
.... RH profile (from P_{GP} and P_{oil})
A: 56.5% RH
B: 73% RH
★ Onset of deliquescence

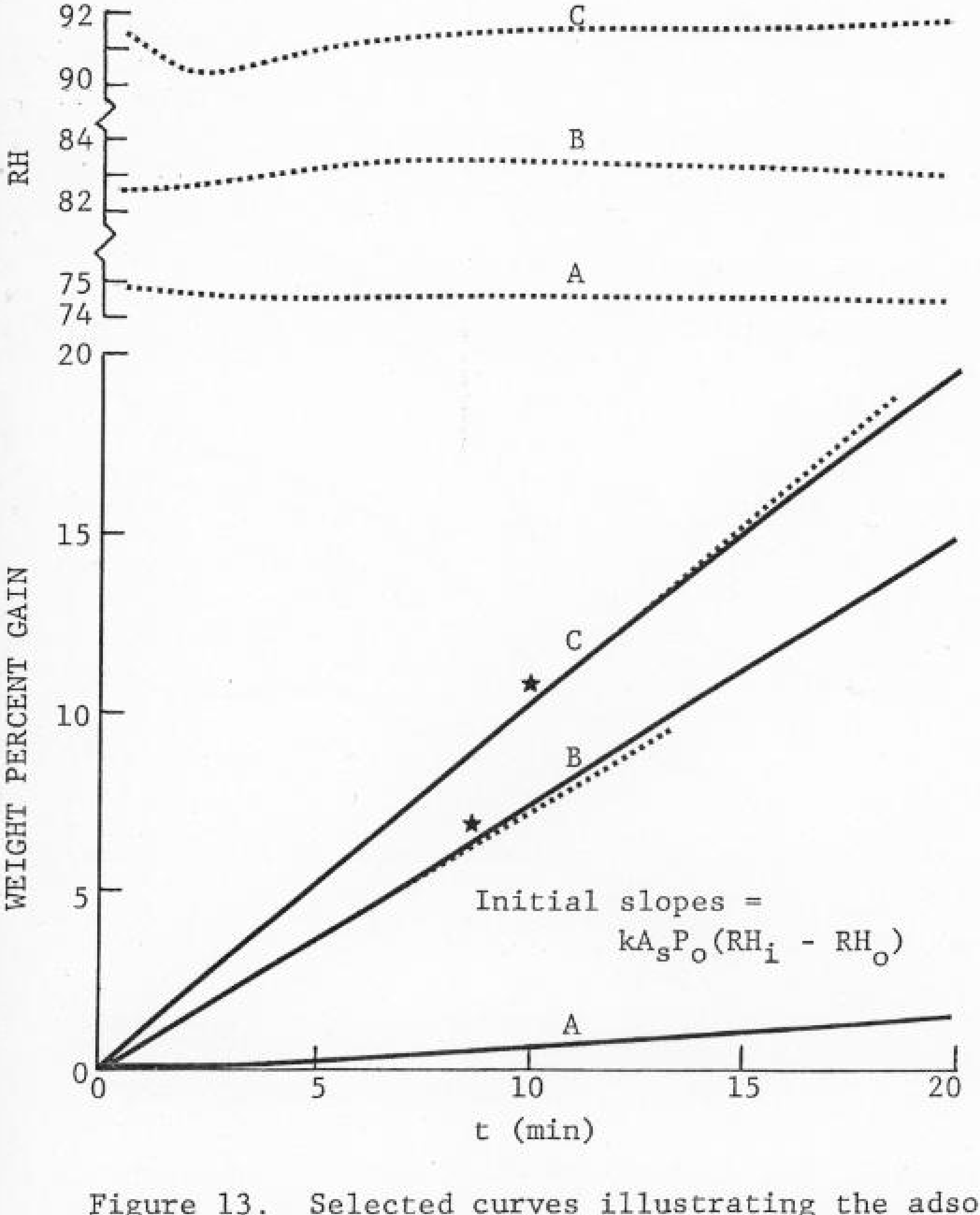

Figure 13. Selected curves illustrating the adsorption of water vapor by choline iodide at 25°C.

<u>KEY</u>: —— Adsorption curve
······· RH profile (from P_{GP} and P_{oil})
A: 75% RH
B: 83% RH
C: 91% RH
★ Onset of deliquescence

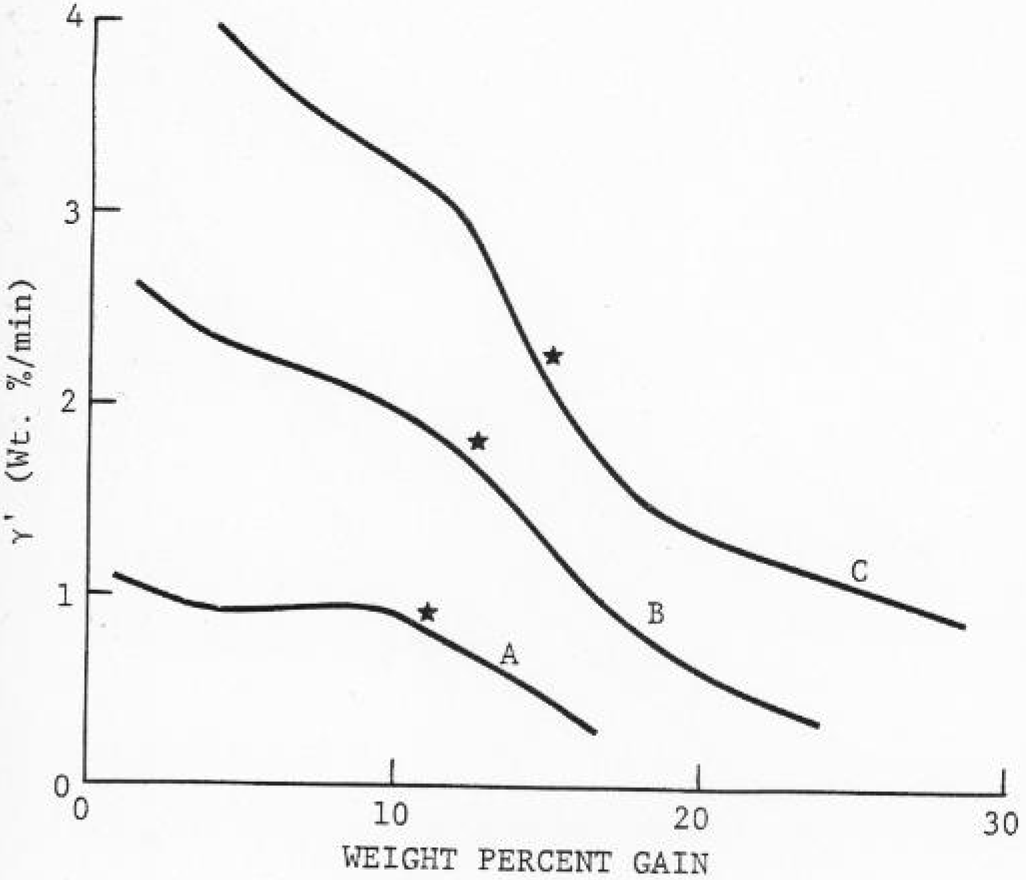

Figure 14. Rate of adsorption by choline chloride at 25^{o}C plotted as a function of weight percent moisture uptake.

<u>KEY</u>: A: 29.5% RH
B: 40.5% RH
C: 54.5% RH
★ Onset of deliquescence

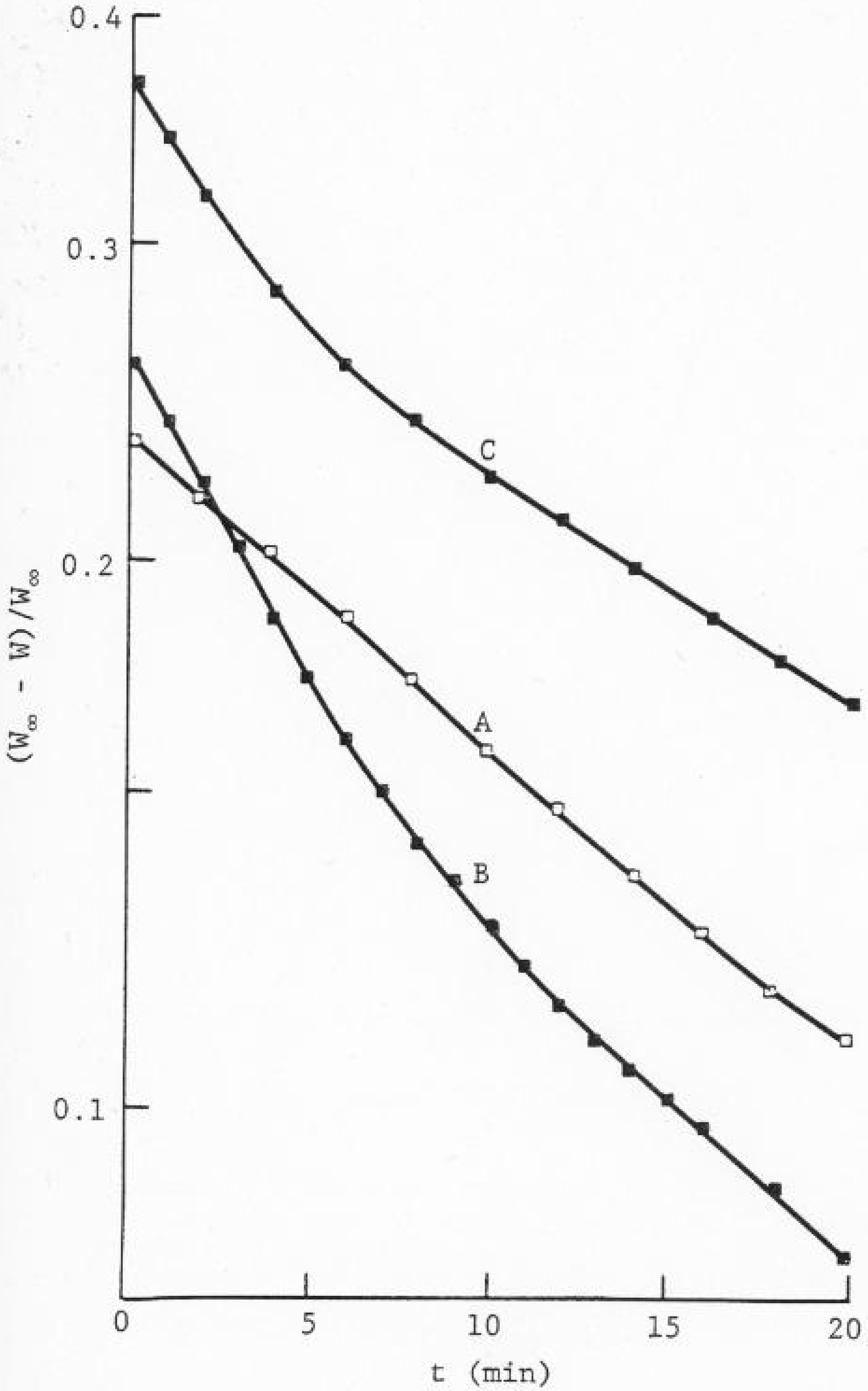

Figure 15. Approach to equilibrium plot of water vapor adsorption by choline Cl at 25°C.

KEY: A: 29.5% RH; B: 40.5% RH; C: 54.5% RH

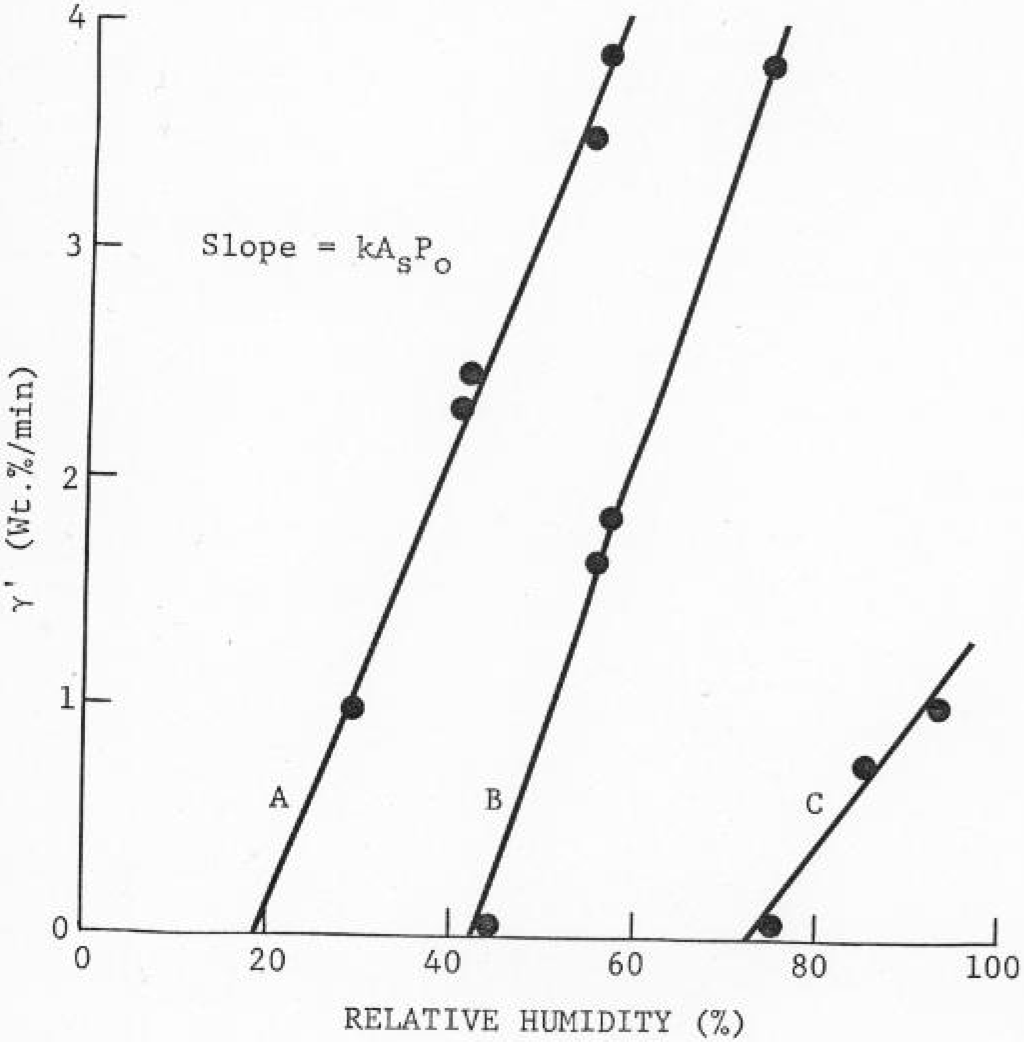

Figure 16. Rate of moisture adsorption by the choline halides at 25°C, plotted as a function of relative humidity.

KEY:
A: Chloride
B: Bromide
C: Iodide

then be achieved by expanding (at the lowest possible ER) from a 92% RH (S_1) atmosphere into V_B and "supporting" immediately with the appropriate "final RH"chamber, i.e. 92, 84, or 74% RH.

DISCUSSION

Instrument Performance

Modifications in the design of the apparatus were successful in optimizing instrument performance as set forth in the "Experimental". The "final RH" on expansion proved to be less predictable than desired, nevertheless a stable RH (± 0.5%) could be reached and maintained within 1-2 min of "zero time" as evidenced by the RH profiles in Figs. 11, 12 and 13. Since the onset of deliquescence did not occur prior to about 5 min, there was a sufficient period ($t \sim 1$-5 min) during which initial uptake rates at steady RH could be monitored. The cause of RH instability during the first minute of adsorption could be attributed primarily to adsorption onto the inside walls of the apparatus which was subjected to varying degrees of degassing during sample preparation. A second likely cause was that of temperature gradients existing over the entire system and affecting RH attainment on expansion. Such gradients were minimized but not eliminated by the shielding used to insulate heat sources. It is suggested that the following additional improvements could be made to insure faster RH stabilization:

(1) Control room temperature more precisely; decrease temperature gradients by forced air circulation over the apparatus.

(2) Stir saturated salt solution RH chambers during use to minimize lag in vapor replenishment due to diffusion in solution.

Other general improvements could include the following:

(1) Maintain the room RH below 40% so as to minimize moisture adsorption by the sample during its loading into the balance chamber.
(2) Reduce capillary length in oil manometer to minimize its lag in response to changes in system RH.
(3) Introduce a means of trapping oil vapor from the oil manometer to reduce the partial pressure of oil within the system.
(4) Monitor sample temperature more precisely by means of a thermistor probe inserted within the sample hangdown tube.
(5) Refine the "sample weight" data by introducing temperature and, more importantly, buoyancy corrections.
(6) Replace stopcocks A and M with "matched" stopcocks to reduce long-term leakage in these areas.

Adsorption Kinetics

Preliminary experiments with the water-insoluble adsorbents, fumed silica and $CaSO_4$, revealed that these materials desorbed moisture readily on changes in atmospheric humidity (Figs. 3 and 4). The ease of sorption reversibility reflected the physical nature of water adsorption by silica. Uptake levels plateaued at moisture contents dependent on the system RH; because of RH instability, however, these curves could not provide any quantitative insight into the adsorption/desorption processes occurring. The deliquescent choline chloride samples exhibited a similar curvilinear, plateauing adsorption profile (Fig.5), but again the RH was not sufficiently controlled for quantitative purposes.

Choline chloride was one of four such deliquescent compounds chosen for examination, the other three being choline bitartrate, bromide and iodide. The bitartrate and chloride salts, both marketed officially as vitamin preparations, are listed as "hygroscopic" and "deliquescent", respectively (265), the latter implying extreme hygroscopicity to the extent of solubilization in sorbed moisture. These salts were studied because their halide series provided a range of hygroscopicities, because they are molecularly simple and because they contain a quaternary ammonium moiety which appears common to many other drugs known to be hygroscopic, such as chloral betaine, acetylcholine chloride, methacholine bromide, tetraethylammonium bromide, and gallamine triethiodide.

Examining the adsorption behavior of choline chloride and choline bitartrate using the "desiccator storage method" yielded moisture adsorption curves similar to those discussed above. The chloride salt deliquesced very rapidly at all but the lowest RH at which negligible adsorption occurred. The bitartrate only deliquesced at 80 and 100% RH, below which it, too, adsorbed only an insignificant amount of moisture. This "all or none" adsorption behavior is characteristic of many soluble substances (242) and can be rationalized in the following way: the critical relative humidity (CRH or RH_o) which exists over a saturated solution of the material determines the minimum RH at which adsorption will occur. Above this RH the material will adsorb water until the adsorbed film is sufficiently dilute for its vapor pressure to be in equilibrium with the atmosphere. For a highly soluble compound this readily leads to complete dissolution or deliquescence, at a rate governed by the difference in RH's (RH_i-RH_o) and by sample size. Once deliquescence has occurred, further moisture uptake depends on the dissolved substance's solution properties, no longer on the "hygroscopicity" of its solid surface. The term "deliquescent" appears reserved, however, for describing those compounds which have RH_o values below normal ambient RH.

As might be expected, there was rank correlation between the initial ($t < 20$ min) uptake rates from the curves in Figs.

6 and 7 and the EMC's taken from these data and plotted in Fig. 8. While the "step" observed in the isotherms for both these salts is typical of specific hydrate formation, subsequent data suggested that this "step" may result from poor precision and is not "real". In fact, EMC values collected from runs conducted on the microbalance were in all cases larger, sometimes considerably, than the data reported in Fig. 8. This can be rationalized by the fact that in the absence of pretreatment (desiccation, etc) a substantial proportion of the EMC of a very hygroscopic material can be picked up during sample preparation and weighing prior to the actual start of the adsorption run. EMC values based on percent weight gain in such cases fall far below the true EMC.

Adsorption experiments performed in vacuo on the modified apparatus permitted more rigorous testing of the kinetic relations proposed by Carstensen (4). As indicated in the "Final Adsorption Experiments" section, the three choline halides were so examined. Their moisture uptake expressed as weight percent gain per minute (γ') at various RH's is given in Figs. 11, 12 and 13. It is apparent from these plots that uptake is approximately linear up to the point of deliquescence. This is even more dramatically demonstrated in Fig. 14 where "breaks" in the curves coincide well with the onset of deliquescence. This is consistent with the notion that the factor RH_i-RH_o in Eq. (2) remains essentially constant, i.e.γ = constant, until deliquescence occurs. At this point the thin film of saturated solution on the crystal's surface is diluted too rapidly to maintain saturation; the RH_o term is then replaced by a function of time, RH(t), reflecting the increasing relative vapor pressure over the increasingly diluted film; and the factor RH_i-RH(t), the driving force for further adsorption, decreases with time until the EMC is reached. The course of adsorption as equilibrium is approached can be described well by the exponential function of Eq. (4). Successful linearization of the whole adsorption curve can in fact be obtained by plotting $\ln\{(W_\infty - W)/W_\infty\}$ vs. t as done for several curves in Fig. 15. Again the biexponential behavior exhibited here is attributable to the change in film surface properties incurred on deliquescence.

It is the initial linearity of the uptake curves, however, that is of primary interest here. Fig. 16 summarizes the initial uptake rates of the choline halides as a function of RH. According to Eq. (2), the slopes of these curves are equal to the product of the "intrinsic" material constant, k, the (constant) vapor pressure of pure water at 25°C (P_o) and the specific surface area A_s (where $A_s = A/W_o$). Accordingly, these curves' linearity depends on a constant A_s for a given material. Since the chloride picked up moisture even under ambient conditions, the A_s for this material could have changed during sample preparation; recrystallization could occur on in situ desiccation, leading to crystal agglomeration and a decrease in the sample's specific surface area. This could easily account for any nonlinearity observed in the data of Fig. 16, especially that of the more hygroscopic bromide and chloride. The nonlinearity of the iodide curve, however, must be rationalized in another way since its surface area is not likely to change under ambient conditions. Assuming the constancy of k, A_s and P_o, the nonlinearity probably evolves from the RH_i-RH_o term in the initial slopes of the adsorption curves in Fig. 13. Perhaps at such high RH's, dissolution of the solid and diffusion to the film surface limits the maintenance of a true RH_o at the surface, depressing the differential pressure driving force.

From the slopes indicated in Fig. 16 and the specific surface areas given in Table II, the "intrinsic" material constants, k, could be calculated for each salt, where the slope (min^{-1}) = kA_sP_o. The values so obtained are given in Table IX. Even though only the geometric surface areas were used to calculate k (since true surface area values were unavailable for all compounds) the rank order of these k values is likely to be valid.

The second significant measure of hygroscopicity that can be extracted from Fig. 16 is that of the halides' RH_o

(or CRH) values. These are determined by the x-intercepts and are also listed in Table IX:

TABLE IX. HYGROSCOPIC PARAMETERS OF THE CHOLINE HALIDES (25°C)

	Cl	Br	I
k(g/cm^2-mm Hg-min)	3.22×10^{-5}	2.21×10^{-5}	6.45×10^{-6}
RH_o (%)	18.5	42	74

On consideration of both parameters, the hygroscopicity of this halide series decreases in the order Cl > Br > I. Significantly, the ratios of these k values are of the same magnitude as the corresponding ratios of the estimated molar solubilities, i.e. the k:molar solubility ratio is approximately equal for all three compounds. This may seem intuitively predictable in that both k and solubility reflect a substance's intrinsic affinity for water. Indeed, an analysis of solubility data of inorganic salts does support this a priori conclusion within a common cation salt series. Interestingly, however, the Na and K halides (except the fluorides) show a reverse trend in solubility and hygroscopicity: for both these series molar solubility increases in the order Cl < Br < I with the corresponding rank decrease in RH_o.

For all these halide series, crystal density increases in the order Cl < Br < I, a fact which complicates the interpretation of crystal lattice effects on the observed hygroscopicities. It has been suggested that the lattice constant is a large determining factor governing the mechanism of adsorption (189). It is possible to calculate theoretically which potential adsorption sites on the crystal surface are most favorable with respect to their potential energy of interaction with an adsorbed water molecule. The nonideality of the lattice surface, however, can prevent the otherwise preferred adsorption to these sites (196). While such basic physical lattice characteristics do contribute greatly to a material's hygroscopic nature, further conclusions about their implications in light of the present data are unwarranted for two reasons: first, not enough is known about the crystal structure of these choline salts, and second, no attempt was made experimentally to control the crystal surface exposed during adsorption.

It is suggested that the chemical affinity of the crystal for water and hence solubility, is more pertinent to the understanding of the present adsorption data. Even the initial slopes in Figs. 11, 12 and 13 represent extensive multilayer adsorption, which is no longer subject to the immediate surface effects of lattice structure. However, the choline cation effects the reverse trend in halide solubility. This same factor probably controls the relative hygroscopicities of the salt series. In a practical sense, it is this macroscopic behavior that is of interest to the formulator. Correlation of k and RH_o values with other properties such as EMC, solubility and density should lend significant insight into the chemical and physical factors governing hygroscopicity. This in turn should lead to better control of the formulation problems brought on by hygroscopic phenomena.

CONCLUSIONS

In contrast to most other "static" methods, the modified adsorption apparatus described here is capable of immediate, sensitive and accurate response to initial moisture adsorption, necessary to the proper study of highly hygroscopic compounds. Lack of precision observed in the data is primarily attributable to other experimental factors, such as sample preparation, which will require better control in future testing. The apparatus proved versatile in its operation with respect to expansion capabilities and ease of component isolation for the purpose of efficient equilibration and evacuation.

The adsorption curves of the choline halides could be linearized using an exponential relation involving equilibrium uptake values. It is suggested, however, that the hygroscopic behavior of the solid surface is best reflected in data collected prior to deliquescence, i.e. the very initial portion of the adsorption curve for a highly hygroscopic salt. This initial moisture uptake appeared to be linear in time (constant slope or rate) at a given RH. In turn, these rates of uptake increased linearly with atmospheric RH (except at very high RH), indicating the predicted proportionality between rate and the difference between the water vapor pressure present and the vapor pressure over the saturated solution of the solid, RH_o.

The uptake rates (Cl > Br > I) at any given RH correlated in inverse order with the observed RH_o values of the halides where $RH_o(Cl) < RH_o(Br) < RH_o(I)$. The intrinsic material constant, k, serves as a proportionality constant relating the uptake rate, γ, to the driving force of the vapor pressure differential. The hygroscopicity of a substance can then be defined by the two parameters, k and RH_o, where increasing hygroscopicity can be associated with increasing k and decreasing RH_o values. The results obtained with the choline halides were consistent with this relationship between the parameters: the ratios of k values were approximately 5:3:1 for the chloride:bromide:iodide, respectively.

Because of the low specific surface area and rapid moisture uptake of the halides, only multilayer adsorption could be observed experimentally. For this reason no conclusions can be drawn with respect to specific crystal lattice effects. The calculated k-values correlated directly with the estimated molar solubilities, however, which suggests that solubility is one of the primary factors controlling hygroscopic behavior of these ionic compounds.

LIST OF SYMBOLS

A	Surface area
A'	Cross-sectional area of Hg manometer tubing
A_{geom}	Geometric surface area (obtained microscopically)
A_s	Specific surface area
A_{true}	True surface area (obtained via air permeametry)
CRH	Critical relative humidity
EMC	Equilibrium moisture content
ER	Expansion ratio
ΔG	Change in Gibbs free energy
h	Height (mm) ΔV_G column
HP	Hygroscopicity potential
k	Proportionality constant, intrinsic material constant
K	Proportionality constant
LR	Leakage rate
MDR	Mass dial range
n	Moles
P	Pressure
P'	Water vapor pressure over saturated solution of compound
P_a	Water vapor pressure in atmosphere
P_o	Water vapor pressure of pure water at given T
P_{GP}	P measured by Convectron gauge
P_{man}	P measured by Hg manometer
P_{MC}	P measured by McLeod gauge

P_{oil}	P measured by oil manometer
P_{p1}	P measured by Pirani electrode #1
P_{p2}	P measured by Pirani electrode #2
R	Gas constant
RR	Recorder range
RH	Relative humidity
RH_i	RH in atmosphere
RH_o	RH over saturated solution of compound
SUBST	Substitution weight
t	Time
T	Temperature
W	Weight (total)
W_o	Initial weight
W_∞	Equilibrium weight
x	Mole fraction
μ	Chemical potential
γ	Moisture sorption rate, dW/dt
γ'	Moisture sorption rate, Wt.% gain/time

Volume regions:

V_B, V_M: Pp. 1-51, refer to Fig. 1; pp. 52ff, refer to Fig. 9

$V_C, V_G, \Delta V_G, V_I, V_J, V_{MC}, V_S$: Refer to either Fig. 1 or Fig. 9

$V_o, V_{P1}, V_{P2}, V_{P3}, V_R, V_{T1}, V_{T2}, S_1, S_2, \ldots, S_7, S_{6A}, S_{7A}$: See Fig. 9

Stopcocks: A-G, I-K: Refer to Fig. 1 or Fig. 9
H: Pp. 1-51, see Fig. 1; pp. 52ff, see Fig. 9
L-R: Refer to Fig. 9

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