[Chem. Pharm. Bull. 16(7)1360—1366(1968)]

UDC 615.31'21'9.011.4

Studies on the Method of Thermal Analysis of Organic Medicinals. VI.[1,2]

Simultaneous Measurement of the Differential Temperature and of the Dielectric Behavior

KEIJI SEKIGUCHI, ISAMU HORIKOSHI, IKUZO HIMURO,
and SOUICHI MIKAMI

School of Pharmaceutical Sciences, Kitasato Memorial University[3]

(Received October 11, 1967)

A new semimicro apparatus for the simultaneous measurement of the differential temperature and the dielectric behavior was constructed and the characteristics of the electric circuits for these physical parameters were discussed. Also, tests concerning dehydration of copper sulfate pentahydrate and glucuronamide monohydrate, polymorphic transition of potassium nitrate and molecular compound formation between aminopyrine and barbital were carried out. The results indicate that the apparatus is sensitive to any one of these phase reactions and is superior to the monofunctional thermal analyzer, especially in that the formation of aqueous solution from a hydrate and the end point of some kinds of phase reactions are more clearly determined.

In order to investigate thermal behaviors of a solid substance, the change in weight, differential temperature, electric conductivity and specific heat are often measured as a function of temperature. Among them, the differential thermal analysis (DTA) is most commonly applied in the field of pharmacy because of simplicity and usefulness of the technique. However, the information only from DTA is not sufficient to know the natures of the phase reactions; therefore, it is desired to measure simultaneously some other physical properties.

In a previous paper, the authors reported a convenient semimicro DTA apparatus suitable for organic medicinals and showed some new applications.[1] The apparatus was then reconstructed by inserting into the DTA sample cell a couple of electrodes for the measurement of dielectric behavior.[4] Thus, two physical properties could be measured simultaneously under visual observation of the sample appearance.

In the present paper, the reliability and applicability of the apparatus were tested with several materials, such as hydrates, a polymorphic substance and a two-component mixture forming a molecular compound, and the results showed that it gave more reliable and wider informations than the usual mono-functional thermal analyzer.

Experimentals

Apparatus 1) Heating Bath and Cells——The cross section of the heating bath is shown in Fig. 1. The lower part is set in an electric furnace. The bath liquid of sulfric acid is stirred by air bubbling from the inlet tube under suction. Double cells modified from those in the previous paper[1] are fixed into the four necks by ground glass settings. One is for the sample material and is inserted with both a thermistor and a couple of electrodes as shown in Fig. 2. Freeze-dried KCl is packed into the rest of the cells. The second one is used for the reference of DTA and the third for the temperature recording. Each of them is introduced with a thermistor. Into the inner tube of the forth cell, a thin thermometer is introduced in such a depth

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[1] Part V: *Chem. Pharm. Bull.* (Tokyo), **12**, 994 (1964).

[2] A part of this work was presented at the 23th Annual Meeting of the Pharmaceutical Society of Japan at Sendai, Nov. 1966.

[3] Location: *Shirokane-Sankocho, Shiba, Minato-ku, Tokyo.*

[4] Since this kind of method had not been hitherto reported, we named it the dielectric behavior analysis (DBA).

that the mercury bulb is buried with KCl powder, and the temperature is also read directly. The heating rate is controlled manually with a voltage transformer. Linear rise is possible by changing the applied voltage in a manner previously determined.

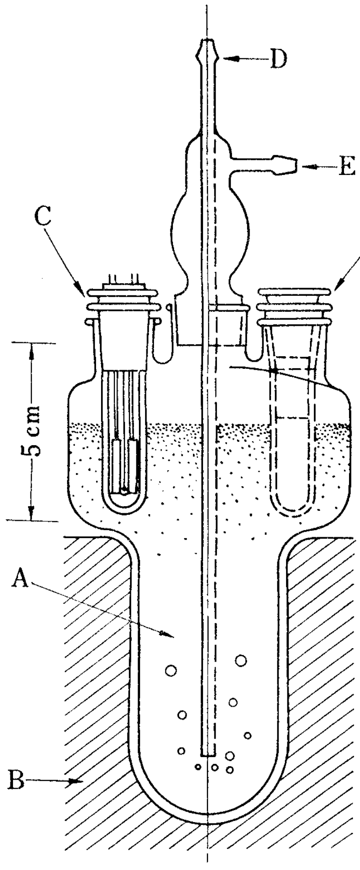

Fig. 1. Heating Bath

A: bath
B: furnace
C: thermistor probe
D: inlet tube
E: outlet tube

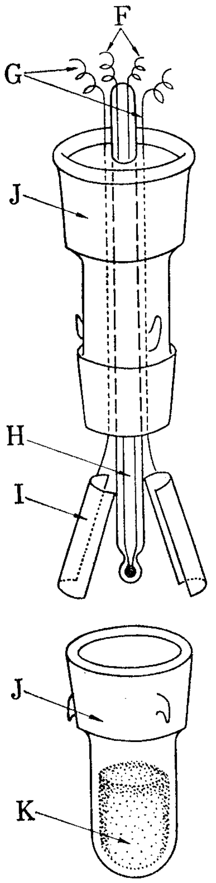

Fig. 2. Construction of the Sample Cell

F: output of thermistor
G: output of electrode
H: thermistor
I: electrode
J: inner tube
K: sample

2) **Electric Circuits**——The block diagram for simultaneous recording of the differential temperature and the dielectric behavior is shown in Fig. 3. For DTA, the temperature difference between the sample and the reference is converted into an output voltage by passing through the thermistor bridge and fed into the recorder.

The change with temperature of the dielectric constant including that of dielectric loss is converted by the phase discriminator circuit into the change of capacity, and is supplied to the recorder after transformation into an output voltage. For the present investigation, a TOA Electronics, Type EPR-3T recorder was used.[5]

Characteristics of the Thermistor Bridge——The bridge circuit for DTA is given in Fig. 4, in which T_1 and T_2 are bead thermistors (Nihon Electric Co., Ltd. Type BT-15, about 100 K-ohm at ordinary temperature), and R_1 and R_2 in the opposing arms are resistances. The resistance values of R_1 and R_2 are equal and any one in the following can be selected: (a) 10.0, (b) 3.0, (c) 1.0 and (d) 0.3 K-ohm. For initial bridge balance, a potentiometer, VR (100 ohm) is used between R_1 and R_2. The current source of the bridge is supplied by a 1.5 volt dry cell (Type FM-3, internal resistance 0.1 ohm).

The linear relation between the logarithm of the thermistor resistance and the reciprocal of the temperature makes it difficult to change the output voltage proportionally to the differential temperature. For

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[5] Characteristics of the recorder were as follows; Range: 5, 10, 25, 50, 100, 250, 500 mV and 1, 2.5, 5, 10, 25, 50, 100 V/semi-scale. Chart speed: 20, 60, 180 mm/hr and 20, 60, 180 mm/min. Pen speed: max. 0.3 sec/full-scale.

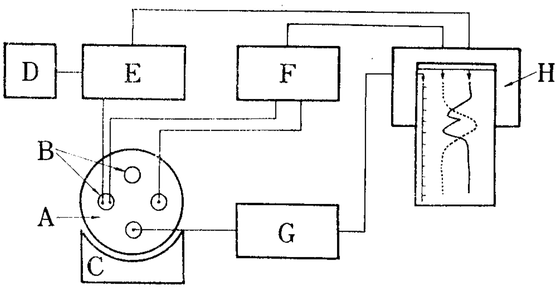

Fig. 3. Block Diagram for Simultaneous Measurement of Differential Thermal Analysis (DTA) and Dielectric Behavior Analysis (DBA)

A: heating bath
B: double tube cell
C: electric furanace
D: X-tal oscillator
E: phase discriminator
F: thermistor bridge
G: thermometer
H: polyrecorder

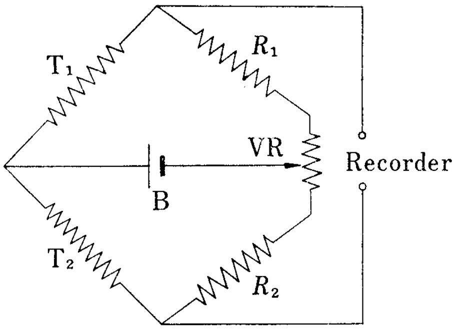

Fig. 4. Circuit Diagram of DTA

VR: 100Ω Potentiometer
R_1, R_2: (a) 10,000Ω±1%
(b) 3,000Ω±1%
(c) 1,000Ω±1%
(d) 300Ω±1%
T_1, T_2: Thermistor-100,000Ω at 25°
(Type BT-15, NEC)
B : 1.5 volt dry cell

this reason, the DTA apparatus adopts usually a bridge circuit of two thermocouples and thermistorization was hitherto infrequently attempted.[6-9] However, if the temperature range of measurement is not wide, the above demerit of the thermistor will be cancelled out by the greater response in resistance with temperature.

The circuit in Fig. 4 was designed to satisfy the requirements for the analysis of organic substances as much as possible. When by an endothermic reaction, the temperature of the sample falls $\Delta T°$ lower than that of the reference, the output voltage of the bridge, ΔV is represented by

$$\Delta V = V_0 R\left(\frac{1}{R+R_{T-\Delta T}} - \frac{1}{R+R_T}\right) \tag{1}$$

where V_0, R, $R_{T-\Delta T}$ and R_T are the terminal voltage of the dry cell, the fixed resistance of each opposing arm ($R=R_1=R_2$), the thermistor resistance for the sample and that for the reference, respectively. Also, in a certain range of temperature,

$$\log R_T = A + B(1/T) \tag{2}$$

in which A and B are constants. Now, if $\Delta T=5°$, the relation between the output voltage ΔV and the temperature is shown in Fig. 5. Each curve has its maximum at a temperature where the ratio R_T/R is unity and the sensitivity or the output voltage will become substantially constant in the vicinity of the maximum. For example, if the experimental error of ±5% is allowable, the temperature ranges of constant sensitivities will be within those represented by arrows in Fig. 5. Also, as shown in Fig. 6, a practically linear relationship could be obtained by calculation between the differential temperature ΔT and the output voltage ΔV; thus, a quantitative determination will be possible with this thermistorized apparatus, if necessary. In this connection, the sensitivity of the DTA circuit of Pakulak, *et al.*[7] in which a parallel shunt is attached to each thermistor was calculated for comparison, and was found to be over 50% less sensitive than that of the above circuit.

Characteristics of the Phase-discriminator Circuit——As shown in Fig. 7, a bridge circuit containing two phase-discriminating tubes in the two arms was employed for dielectric behavior measurement. To each of the first grids of the tubes, a signal of the same phase (455 kc) is supplied and the dielectric change of the sample is detected by a LC circuit which is parallel to the cell and is connected to the third grid of one of the tubes; thus, the change in capacitance is converted into the voltage change, as shown by the working characteristic curves in Fig. 8. Near the point of resonance, strict linearity is maintained between the capacitance and the output voltage. In the case of extremely large cell resistance and/or cell impedance, the voltage changes about 20 V by a change in capacitance of 1 $\mu\mu$F; however, when the resistance between cell electrodes is diminished, the capacitance dependency of the output voltage is lowered as shown by cruves (b), (c) and (d) in the figure, since the Q-value of the resonance circuit becomes much decreased. Accordingly, a quantitative

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6) M. Inoue and T. Saito, *Yakugaku Zasshi*, **80**, 693 (1960).
7) J.M. Pakulak and G.W. Leonard, *Anal. Chem.*, **31**, 1037 (1959).
8) S. Fara, *Drumysl Potravin*, **13**, 609 (1962) [*C.A.*, **58**, 4177 (1963)].
9) M.J. Joncich and D.R. Bailey, *Anal. Chem.*, **32**, 1578 (1960).

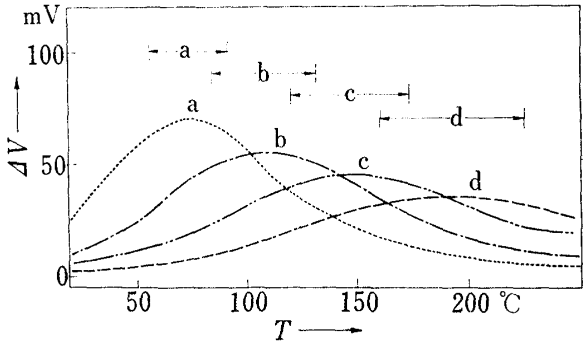

Fig. 5. Relationship between the Output-voltage of Thermistor Bridge and Temperature

·············· (a): $R=10000\Omega$, range=56°—92°
—·—·— (b): $R=3000\Omega$, range=88°—130°
—··—··— (c): $R=1000\Omega$, range=122°—175°
- - - - - (d): $R=300\Omega$, range=164°—230°

a) Within the error of 5%, output-voltage (Sensitivity) is constant in this range.

b) When the temperature difference (ΔT) between bridge thermistor T_1 and T_2 is 5°, the cruves of output-voltage (ΔV) is calculated from the equation; $\Delta V=V_0R\cdot[1/(R+R_{T-\Delta T})-1/(R+R_T)]$.

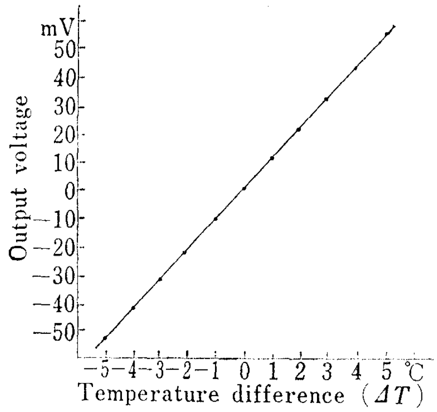

Fig. 6. Relationship between the Temperature Difference (ΔT) of a Couple of Thermistor and the Output Voltage (ΔV) of Bridge Circuit

estimation will be possible, so long as the resistance of the sample remains nearly constant and the change in capacitance does not exceed the linear portion of the working characteristic curve. However, if an abrupt decrease in resistance is occurred, the apparent dielectric constant decreases markedly, so that it becomes difficult to recognize whether it is due to the change in dielectric constant or in dielectric loss. Even in such a case, the measurement is possible by diluting the sample previously with a powder of inert material. As shown later, such a circuit property affords a useful aid for the assignment of DTA peaks in the dehydration of hydrates.

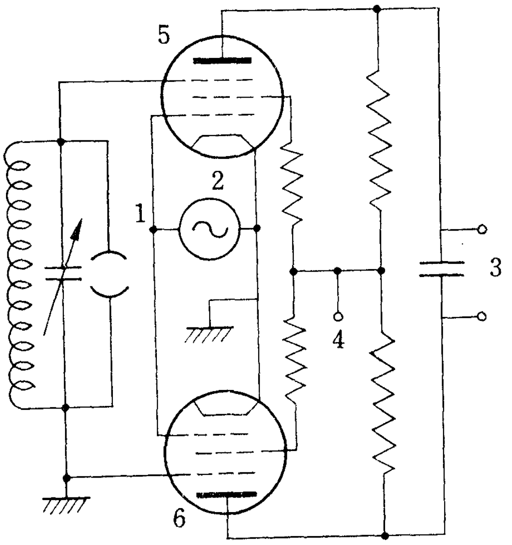

Fig. 7. Circuit Diagram of Phase Discriminator

1: cell 2: input 455 kc 3: output
4: B+(230 Volt D. C.) 5,6: 6BN6

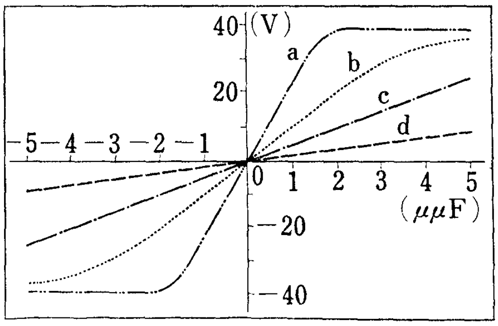

Fig. 8. Voltage Characteristics of Phase Discriminating Circuit

Leak resistance of Cell at 455 kc
a —··—··— ∞Ω
b ·············· 100 kΩ
c —·—·— 30 kΩ
d - - - - - - 10 kΩ

Sample Materials——$CuSO_4\cdot 5H_2O$: G.R. grade chemical was recrystallized twice from water and is ground to a fine powder. Glucuronamide ($C_6H_{11}O_6N\cdot H_2O$): The aqueous solution of the commercial product was treated with active charcoal. The crystals obtained after evaporation of the filtrate was purified twice by recrystallization from aqueous methanol and then air-dried. KNO_3: G.R. grade chemical was used without further purification. Aminopyrine and Barbital: Both were commercial products of J.P. grade.

Results and Discussion

Dehydration of Copper Sulfate Pentahydrate

In the previous paper, the dehydration process of this salt hydrate was investigated by DTA and it was found that the fall and rise in the curve correspond well with the color change of the sample. In the present investigation, the same process was examined by the simultaneous DTA–DBA measurement in order to confirm the previous assignments of the DTA–peaks.

When the pentahydrate was used without dilution, both the DTA– and the DBA–curve are represented by I and I′ in Fig. 9. From about 80°, increase in the apparent dielectric constant and the departure of the DTA–curve from the baseline become noticeable. As the temperature rises to 98°, the DBA–curve increases rapidly; whereas, the beginning of the corresponding fall of the first DTA–peak delays by several degrees. At a temperature a few degrees higher than 100° where the DTA–curve still continue to fall to the first peak maximum, the apparent dielectric constant falls abruptly down and becomes nearly constant up to the temperature of the second steep rise where the corresponding DTA–curve just passes through the second peak. Within the temperature range of constant response in the DBA–curve, liquid formation is visually observed. The third DTA–peak near 130° is attributed to conversion from the tri– to the mono–hydrate. The same change is represented by the third increase in the DBA–curve.

These results can be reasonably understood by the following interpretation. From about 80°, decomposition of the pentahydrate not accompanied with condensation of the dissociated vapor begins to cocur in a small degree, and the stage will continue until the temperature at which the first rapid rise in the DBA–curve appears. Since the dielectric constant of liquid water is greater than that of vapor, this rise will be attributed surely to formation of solution. In other words, the peritectic point or the transition point of the pentahydrate will be reached. The corresponding endothermic fall in the DTA–curve is however, delayed by about 5°. This will be resulted by the fact that the endothermic heat effect due to dissociation of two molecules

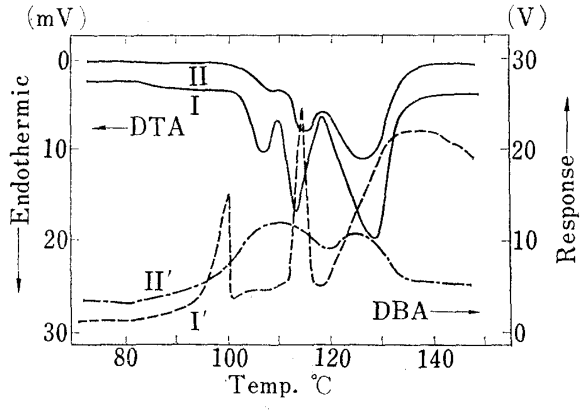

Fig. 9. Simultaneous DTA–DBA Curves of $CuSO_4 \cdot 5H_2O$

Experimental conditions

No.	I(DTA), I′(DBA)	II(DTA), II′(DBA)
Heating rate	1.5°/min	1.5°/min
Sample amount	45.0 mg	130 mg (20% mixture with Al_2O_3)

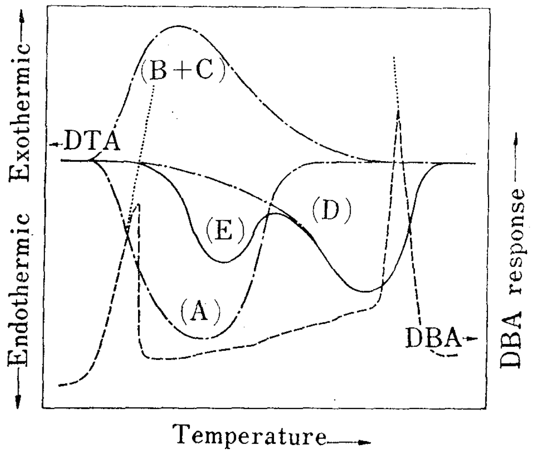

Fig. 10. Schematic Diagram of Various Heat Effects involved in the Dehydration Process of $CuSO_4 \cdot 5H_2O$ to $CuSO_4 \cdot 3H_2O$

$(CuSO_4 \cdot 5H_2O)$
$\downarrow$ A: endothermic reaction
$(CuSO_4 \cdot 3H_2O) + 2H_2O$ (gas)
$\downarrow$ B: exothermic reaction
$(CuSO_4 \cdot 3H_2O) + 2H_2O$ (liquid)
$\downarrow$ C: exothermic reaction
$(1-x) \cdot (CuSO_4 \cdot 3H_2O) + x \cdot CuSO_4$ soltuion
$\downarrow$ D: endothermic reaction
$(CuSO_4 \cdot 3H_2O) + 2H_2O$ (gas)
Curve E is the summation of A—D.

of water is largely counterbalanced with the exothermic one caused by condensation of the dissociated vapor; thus, the total heat effect is recorded in the curve behind the DBA–peak, as shown in the schematic diagram in Fig. 10.

As the amount of the liquid condensed is increased, a bridge is formed between the two electrodes. At this temperature, the DBA–curve breaks suddenly down as the result of resistance decrease, though the DTA–curve still continue to fall to the maximum of the first peak which is indicative to decomposition of the pentahydrate. Since evaporation of the solution formed follows after the peritectic reaction, the second DTA–peak is assigned to this endothermic effect. This process is also visually observed by a gradual disappearance of the liquid phase and by color change from intense blue to light green. In the earlier stage of evaporation, the two electrodes are bridged by the solution; however, once the brdige is cut off, a sudden rise is recorded in the DBA–curve. As mentioned in the previous paper, a small shoulder sometimes appears in the beginning of the first DTA–peak. This will probably be a sign that the condensation reaction is incidentally retarded. Also, in other cases, the peritectic reaction is shown by a shoulder in the DTA–curve in place of the first peak. The fact that the change from the tri– to the monohydrate is represented by a single peak in DTA and by a step in DBA suggests that the vapor dissociated in this process will not condense.

When the sample is diluted with alumina powder, both the DTA– and DBA–curves are shown by II and II′ in Fig. 9. Because the diluent absorbs vapor and liquid water, the bridge of solution between the electrodes is not formed; therefore, the steep rise and fall in the DBA–curve disappear completely and smooth hills appear instead.

Dehydration of Glucuronamide Monohydrate

When the hydrate itself was used and a relatively slow heating rate was maintained, the DTA– and the DBA–curve are given by I and I′ in Fig. 11. The initial fall at about 80° in the DTA–curve corresponds to the beginning of peritectic reaction and the subsequent exothermic peak is attributable to both condensation of the dehydrated vapor and crystallization of the anhydrous compound. The second endothermic peak will occur as the result of evaporation from the solution. As shown in Fig. 10, the pattern of the curve will indicate that the process of dehydration is composed of several elementary reactions. In the DBA–curve, two peaks are given. The small abrupt fall in the first peak is the sign of formation of liquid phase. Since glucuronamide is a non-electrolyte, it is natural that a marked change in the Q–value will not occur even at the moment the two electrodes are connected or disconnected with its solution.

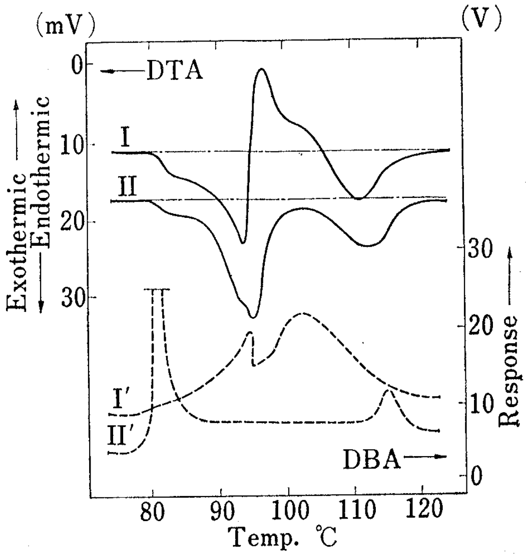

Fig. 11. Simultaneous DTA–DBA Curves of Glucuronamide·H_2O

No.	I(DTA), I′(DBA)	II(DTA), II′(DBA)
Heating rate	1.0°/min	2.0°/min
Sample weight	100 mg	110 mg

a) In sample of No. II, about 10% of KCl is added.

If the hydrate is mixed with a small amount of KCl (10%), a sharp peak due to formation of the electrolyte solution is produced at 78° resembling to the first stage of dehydration of copper sulfate pentahydrate (I′ in Fig. 9). The above assignments are also supported by visual observation.

Polymorphic Transition of Potassium Nitrate

In order to examine the applicability of the apparatus to the detection of polymorphic transition, heating and cooling curves of KNO_3 were taken and the results are shown in Fig. 12.

In the heating process, an endothermic peak and an increase in the dielectric constant appear at the same temperature of 129°. From the shape of the DBA–curve, it is seen that blunting of the Q–value does not occur during transition. Although the point of completion of reaction can not be determined by DTA, it is clearly indicated in the DBA–curve by the point at which the upper step is just arrived.

When the sample is cooled under a constant rate, the transition is suspended appreciably by molecular hysteresis. Also, the DTA–curve gives two exothermic peaks and the corresponding DBA–curve shows an intermediate step. The fact will suggest that some other kind of polymorphic structure is present or that the transition reaction is again retarded at this range of temperature by some unknown reason.

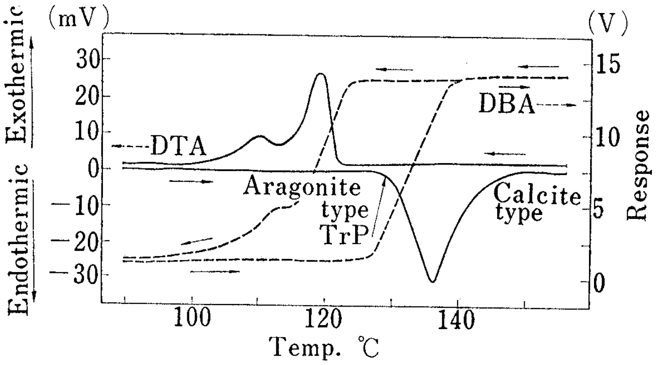

Fig. 12. Simultaneous DTA–DBA Curves of KNO_3 (Aragonite⇄Calcite type structures)

→temperature increase
←temperature decrease
transition point: 129°
heating rate: 1.5°/min
sample weight: 53.0 mg

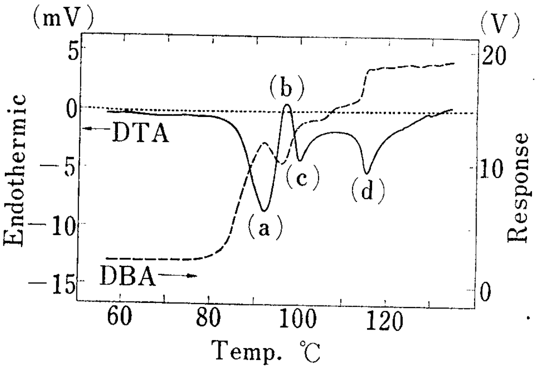

Fig. 13. Simultaneous DTA–DBA Curves of Aminopyrine–Barbital Physical Mixture

mole ratio: 1:1
heating rate: 1.5°/min
sample weight: 83.0 mg
(a): metastable eutectic liquefaction
(b): molecular compound formation and solidification of metastable liquid
(c): eutectic liquefaction
(d): peritectic reaction or metastable melting

Molecular Compound Formation between Aminopyrine and Barbital

In Fig. 13, results obtained with an equimolar physical mixture of both components are given. As have been discussed in the preceeding paper, the first endothermic peak and the subsequent exothermic one is attributed to the metastable eutectic liquefaction and to both the molecular compound formation and the solidification of metastable liquid. The second endothermic peak appears due to the eutectic liquefaction, though it is also metastable in respect of the composition of the whole mixture. The third one will be assigned either to the peritectic reaction or more probably to the metastable melting caused by retardation of the former. Corresponding to these DTA–peaks, changes in the DBA–curves are observed. Solidification of the liquid formed by the metastable eutexia is recorded in the curve as a decrease of the apparent dielectric constant.