

Figs. 1 and 3 arise from exponential equations only, *i.e.*, there are no zero-order rate constants involved. The curves are nearly linear for almost 50% of the ordinate scale. This phenomenon, and its implications in relation to recent publications concerning parallel zero-order and first-order kinetics (2, 4) will be the subject of a separate publication (6).

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## Quantitative Evaluation of the Heat-Stabilizing Properties of Organotin Compounds in Rigid Polyvinyl Chloride Using Differential Thermal Analysis

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Rigid polyvinyl chloride bottles are in current use in Europe for a host of products including foods, drugs, and cosmetics. In this country, a number of pharmaceutical and cosmetic firms are exploring the possibilities of this plastic container for packaging of one or more products. Presently, a number of vinyl systems are effectively stabilized against thermal and radiation degradation by the use of organotin compounds. In order to ascertain the efficiency of organotins to stabilize rigid vinyls, a quantitative study was undertaken on a series of vinyl formulations containing various organotin compounds using differential thermal analysis. These techniques proved to be extremely helpful in evaluating the materials from both a qualitative and quantitative point of view. Furthermore, the same techniques appear to have great promise in predicting the most suitable plastic formula for achieving the most stable plastic item when thermal or radiation damage becomes a potential problem.

ONE OF THE most widely used polymers in the medical science field is polyvinyl chloride (PVC). Its primary application has been in the construction of blood bags, surgical tubings, containers for biological products, catheters, and a host of other items. As is well established, vinyl resins are inherently unstable materials and are prone to thermal and oxidative degradation (1). This instability is primarily due to the imperfections and anomalies on the polymer chain, such as unsaturated chain endings and chain branching and to certain incorporated oxygen functions such as hydroperoxy groups. During the heat processing and throughout the active life of the polymer, these structural abnormalities will be the initiating points of the degradation process. In 1936, Yngve discovered that certain organotin compounds proved effective in minimizing the deterioration of PVC (2). During the past 20 years hundreds of structurally modified organotin compounds have been used as PVC heat and light stabilizers. Much has been

written on their mode of action, but even up to the present time no generally agreed theory has evolved.

Within the past several years, great commercial interest has been shown in the development of the clear, colorless, rigid polyvinyl chloride bottles which now enjoy a great deal of success in Europe as food and drug containers. Generally, it has been found that the organotin compounds are the most efficient stabilizers for the clear, colorless bottles, even though some question of toxicity may be raised if the organotin compound would be leached into a product (3). Extraction tests following generally accepted procedures, however, have demonstrated that the rigid vinyls have little propensity to release a constituent to an extracting medium, and thus the safety of the bottle may be quite acceptable for any intended drug or cosmetic use.

Since the stabilizers play a key role in producing an acceptable rigid polyvinyl chloride, and since the organotins appear to be in general the most suitable stabilizers, it was decided to undertake a study using differential thermal analysis to evaluate which of a group of organotin compounds might give the greatest protection against thermal degradation. As will be demonstrated, differential thermal analysis proved

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a very useful tool in deducing quantitatively the most suitable formula in a relatively short period of time.

## EXPERIMENTAL

**Materials and Apparatus—Polyvinyl Chloride—**The PVC's used are listed with their corresponding weight average molecular weights.<sup>1</sup>

PVC Identification	Wt. Av. Mol. Wt.
PVC 65.....	62,000
PVC 105.....	83,000
PVC 161.....	91,000
PVC 120.....	107,000
PVC 123.....	114,000

**Organotin Stabilizers—Di-*n*-butyltin diacetate, di-*n*-butyltin  $\beta$ -mercaptopropionate, di-*n*-octyltin  $\beta$ -mercaptopropionate, di-*n*-butyltin diisooctylthioglycolate, and bis-(di-*n*-butyltin monolauryl maleate) (Advance Division, Carlisle Chemical Works, Inc., New Brunswick, N. J.). Di-*n*-butyltin dilaurate, and di-*n*-butyltin maleate (M & T Chemicals, Inc., Rahway, N. J.). Di-*n*-butyltin diisooctyl maleate and di-*n*-butyltin dilauryl mercaptide (Cardinal Chemical Co., Columbia, S. C.).**

**Polyvinyl Chloride Films—**In those cases where stabilizers are used, the polymer (600 Gm.) and the stabilizer (in the desired concentration) are placed into a 1-gal. laboratory Hobart mixer<sup>2</sup> and mixed for 30 min. The films of the polymers are prepared by milling them on a Farrell-Birmingham mill<sup>3</sup> having a chromium plated variable-speed roller. Prior to milling each film, the mill's rollers are carefully cleaned with practical grade stearic acid.<sup>4</sup> The temperature of the rollers is maintained at 175° and the duration of the milling is 5 min. During the final phase of the operation, the separation of the rollers is adjusted to furnish films having thicknesses in the range of 0.040–0.045 in. Cut samples 5<sup>7</sup>/<sub>8</sub> × 5<sup>7</sup>/<sub>8</sub> in. from the milled stock are then press polished on an electrically heated compression press<sup>5</sup> with platens cored for water cooling. The molds containing the samples are then heated for 3.5 min. at 35,000 lb. of pressure and rapidly cooled to 120° before removing the test sample from the mold. All samples are finally allowed to condition at room temperature and 50% relative humidity for 48 hr. prior to their use.

**Differential Thermal Analysis Apparatus (DTA)—**The apparatus consists of a combined controlled atmosphere differential thermal analyzer and effluent gas analyzer model KA-2-HD with a quick-cool furnace model F-1DF, and two L&N Speedomax H strip chart recorders. This instrument is manufactured and described by Robert L. Stone Co., Austin, Tex. (4, 5).

The sample holder assembly, model SH-M4CAZ, consists of two separate, circular Platinel differential thermocouples and a Chromel-Alumel furnace couple which is utilized for programming as well as recording the temperature of the furnace. The sample holder and recorder system permit the re-

coding of two separate thermograms simultaneously. The recorder is linear in time only and has a chart speed of 1.0 in./min. The sample and reference compartments are cylindrical aluminum pans with a diameter of 3.5 mm., a depth of 1.5 mm., and a weight of 1.4 mg. The temperature scale of the instrument is calibrated using the known crystallographic inversion temperature of ammonium thiocyanate (88°) and the melt transition temperature of tin (231.8°). The heat transfer coefficient for the differential thermocouple is determined by utilizing the heat of fusion of tin (14 cal./Gm.). The calibration is performed utilizing a linear programming rate of 12.6°/min. and nitrogen as the dynamic gas to prevent any oxidative effects. The material under study is placed in the sample container and no reference material is used. The *K* value determined is  $3.09 \times 10^{-7}$  cal./mm.<sup>2</sup>. Various range settings of the d.c. amplifiers provide identical *K* values. All areas are measured in triplicate with a plane planimeter and the results are averaged.

**Effect of Molecular Weight on Transition Temperatures—**In order to establish certain standards or guidelines in regard to temperatures at which transitions occur in polyvinyl chlorides of the different weight average molecular weights, samples of each of the polymers were run in the differential thermal analysis instrument at a heating rate of 6.0°/min. Highly calcined, 80-mesh alumina (Al<sub>2</sub>O<sub>3</sub>) was used as the reference. In all determinations exactly 1-mg. samples were employed. Nitrogen was the dynamic gas on the DTA runs, and helium was used for the effluent gas analysis.

Figure 1 illustrates a typical thermogram with the several transition temperatures. It will be noted that two transition temperatures are evident. The lower transition temperature may be considered as the glass transition temperature and may further be referred to as the main glass transition temperature (*T<sub>g</sub>*). These *T<sub>g</sub>* values for the various molecular weights are shown in Table I and reveal that this transition temperature increases from 80.9° for the lowest molecular weight (62,000) to a high of 87.3° for the highest molecular weight (114,000). A second transition temperature, which presently will be referred to as a depolymerization transition temperature (*T<sub>d</sub>*), is seen at 200.6° for all of the polymers, regardless of weight. From the various thermograms, it was possible also to evaluate the peak temperature at which dehydrohalogenation took place as well as calculate the standard heat of transition of  $\Delta H^\circ$  for the dehydrohalogenation process. The method of calculation for  $\Delta H^\circ$  is included under *Appendix*. These values and constants are also included in Table I, and it appears that as the weight average molecular weight increases, the polymer has greater thermal stability. This is, however, an assumption since there are some polymers which show better thermal stability to active burning and produce thermograms that indicate a lower decomposition temperature. The reason for this is that some combustibles or non-combustibles are released at a lower temperature; a protective char is formed on the surface of the polymer which prevents further active burning.

Figure 2 illustrates the thermograms of the dehydrohalogenation transitions of the polymers studied. It should be noted that the lower molec-

<sup>1</sup> PVC is trademarked as Vygen by the General Tire & Rubber Co., Akron, Ohio, who also supplied the weight average molecular weight data.

<sup>2</sup> Model K 45, Hobart Mfg. Co., Troy, Ohio.

<sup>3</sup> Farrell-Birmingham Co., Ansonia, Conn.

<sup>4</sup> Eastman Chemical Co., Rochester, N. Y.

<sup>5</sup> Duke Corp., model 44-325, Grand Haven, Mich.

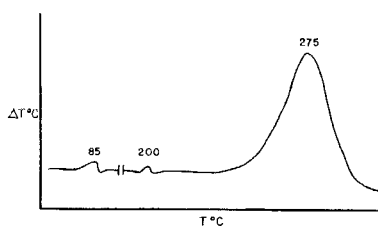


Fig. 1—Differential thermal analysis thermogram of polyvinyl chloride in a nitrogen atmosphere.

TABLE I—EFFECT OF MOLECULAR WEIGHTS ON TRANSITION TEMPERATURE AND DEHYDROHALOGENATION PROCESS OF POLYVINYL CHLORIDES

Wt. Av. Mol. Wt.	Glass Transition Temp., °C.		Dehydrohalogenation		Effluent Gas Peak, mm. <sup>2</sup> /mg. of Sample
	$T_g$	$T_i$	Peak Temp.	$\Delta H$ (Kcal./mole)	
62,000	80.9	200.6	275.9	20.3	212
83,000	82.8	200.6	282.1	25.8	267
91,000	83.9	200.6	283.2	29.2	300
107,000	85.8	200.6	284.6	30.4	330
114,000	87.3	200.6	285.2	33.2	369

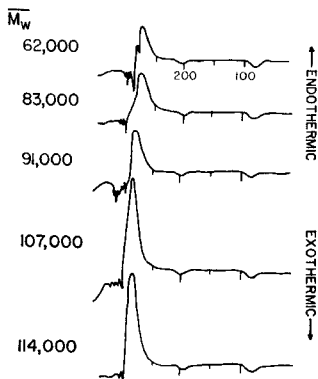


Fig. 2—The effects of molecular weight on the polyvinyl chloride thermogram.

ular weight polymers have their HCl evolution transitions interrupted by multiple exothermic reactions typical of bond scission. The higher molecular weight polymers do not reveal this type of polymer chain degradation, but merely exhibit large dehydrochlorination endotherms.

As each of the samples were run, there was a simultaneous recording of the effluent gas evolution, and as may have been anticipated, the greater the molecular weight, the greater will be the volume of HCl released for a unit weight of polymer. The quantity of HCl released with each polymer is included in Table I but is expressed as the area under the curve rather than in units of volume.

**Effect of a Group of Dialkyltin Stabilizers on Glass Transition Temperatures**—A series of experiments was conducted with a group of organotin compounds at three different concentrations (1.5, 3.0, and 5.0 p.h.r.) using one molecular weight polymer (114,000). The highest molecular weight polymer

TABLE II—EFFECT OF DIALKYL TIN STABILIZERS ON GLASS TRANSITION TEMPERATURE OF A POLYVINYL CHLORIDE (114,000)<sup>a</sup>

Stabilizer	Concn. Level In Polymer	Transition Temp., °C.
Dibutyltin diacetate	1.5	83.3
	3.0	81.5
	5.0	74.1
Dibutyltin diisooctyl thioglycolate	1.5	80.3
	3.0	75.8
	5.0	71.3
Diocetyl tin $\beta$ -mercaptopropionate	1.5	83.7
	3.0	84.8
	5.0	83.9
Dibutyltin $\beta$ -mercaptopropionate	1.5	82.6
	3.0	84.3
	5.0	85.5
Dibutyltin diisooctyl maleate	1.5	81.5
	3.0	78.7
	5.0	73.6
Bis(dibutyltin mono-) lauryl maleate	1.5	81.9
	3.0	78.1
	5.0	76.9
Dibutyltin dilauryl mercaptide	1.5	88.7
	3.0	77.0
	5.0	72.9
Dibutyltin dilaurate	1.5	79.1
	3.0	76.4
	5.0	76.9
Dibutyltin maleate	1.5	83.9
	3.0	82.6
	5.0	81.9

<sup>a</sup>  $T_g$  of pure polymer is 87.3°C.

was used in this case because the previous experiment demonstrated that the most thermally stable polymer was the polymer having the weight average molecular weight of 114,000. The glass transition temperatures for these formulations have been included in Table II. In every case except one (dibutyltin dilauryl mercaptide at 1.5) the glass transition temperature was reduced below the 87.3°  $T_g$  for the pure polymer. Furthermore, the decrease continued as the concentration of the stabilizer was increased. These  $T_g$  values demonstrate that for this group of stabilizers, a plasticizing effect is noted, and that the extent of plasticization is dependent upon the compound and its concentration.

**Effect of a Selected Group of Dialkyltin Stabilizers on Dehydrohalogenation**—Since the main purpose of heat stabilizers is to prevent or retard degradation of polymers when exposed to heat, differential thermal analysis was conducted on polyvinyl chloride films containing two concentrations of a specific organotin compound. In these films only the lowest molecular weight (62,000) polymer was used since, as has been revealed before, this material has the least thermal stability of the group of polymers studied. Four organotin compounds were used and these were based upon those which have or are known to be the most used compounds in vinyl formulations requiring a high degree of heat stability. From the various thermograms, the onset temperature of dehydrohalogenation and the temperature of peak degradation were found. Heats of dehydrohalogenation were also calculated and, from the effluent gas recording, the peak area of gas evolved was evaluated. All these values or constants are included in Table III.

TABLE III—EFFECT OF SELECTED DIALKYL TIN STABILIZERS ON THE DEHYDROHALOGENATION OF POLYVINYL CHLORIDE

Stabilizer	Concn.	Onset of Transition, °C.	Peak Transition, °C.	Heat of Transition, cal./Gm.	Peak Area of Effluent Gas Analysis, mm. <sup>2</sup> /mg. of Sample
Pure polymer	0	221.0	275.9	20.31	212
Dibutyltin diisooctyl thioglycolate	1.5	266.3	284.3	13.17	
	3.0	271.2	285.2	11.58	370
Diocetyl tin β-mercaptopropionate	1.5	263.3	284.8	15.80	
	3.0	258.7	290.4	12.89	300
Dibutyltin β-mercaptopropionate	1.5	261.4	284.3	18.03	
	3.0	276.5	287.6	15.17	360
Dibutyltin maleate	1.5	276.8			
	3.0	277.2		<sup>a</sup>	400

<sup>a</sup> Thermogram produced multiple endo- and exotherms from 276.8° to 326.3°C.

## DISCUSSION

Differential thermal analysis permits the evaluation of a final plastic material such as polyvinyl chloride and allows in a relatively short period of time an assessment of how a number of parameters will influence the final product. In the case of this report differential thermal analysis was conducted under an inert environment (nitrogen) to eliminate oxidative effects.

As Table I shows, the main glass transition temperature increases with an increase in molecular weight. This results from a decrease in the polymers' fractional free volume. Generally, the glass transition temperature is considered as that point in the temperature scale where a material will be glass-like (below  $T_g$ ) or rubber-like (above  $T_g$ ). Perhaps a better way to think about the glass transition temperature is that as the  $T_g$  decreases a more pliable material will result.

Increase in the molecular weights of the pure polymers (Table I) had very profound effects upon retarding the dehydrohalogenation of the polymer. The dehydrohalogenation transition can be considered as the temperature where rapid polymer degradation starts to take place and thus may be related to the stability of the polymer. As may be seen from Table I, the heat requirement for dehydrohalogenation is increased by 13 cal./Gm. when the molecular weight of the PVC is increased from 62,000 to 114,000. In applications where heat treatments (for example to produce a certain device) reach temperatures above normal processing conditions, a higher molecular weight polymer will be the most suitable, providing all other factors are constant.

As has been reported before (see Table II), various organotin compounds incorporated in a specific polyvinyl chloride will reduce the glass transition temperature. The ability of these compounds to influence the  $T_g$  may on occasions be beneficial as for example when there is a need for a more ductile plastic, but without the desire to add any plasticizer. In this case, the addition of dibutyltin diisooctyl thioglycolate reduced the  $T_g$  from 87.3°, for the pure polymer, to 80.3° at a 1.5 concentration or to 71.3° for a concentration of 5.0. Compare the values just quoted to those values for dioctyltin β-mercaptopropionate. At a concentration of 1.5 the dioctyltin β-mercaptopropionate reduces the  $T_g$  to 83.7°, but further increase of the stabilizer

to 3.0 or 5.0 has little additional effect on the  $T_g$ . These decreases in  $T_g$  may be attributed to a plasticizing effect on the polymer such that an increase in fractional free volume results (6,7).

Differential thermal analysis also was very valuable in conveying at which temperatures rapid dehydrohalogenation of the polymers will occur with some of the most widely used organotin compounds. As can be seen in comparing the compounds in Table III, in each instance the tin compounds were able to increase the temperature of dehydrochlorination from 221° for the pure polymer to values of above 260° (approximately). An interesting result, not readily explainable, is the reduction of the heat of dehydrohalogenation from 20.3 cal./Gm. to values of nearly half. In other words, these values ( $\Delta H$ ) indicate that once the plastic has reached a temperature where rapid dehydrohalogenation is to commence, less energy will be needed to bring about the degradation. The authors have reported this same phenomenon when different plasticizers were added to PVC (8).

The analysis of the data gathered from the use of the differential thermal analysis instrument for the limited number of polymers reported in this paper demonstrates that the technique can become a powerful tool for laboratories wishing to evaluate the stability of plastic materials, particularly the vinyl types. The results of the experiments reported here confirm the ability of organotin compounds to protect rigid polyvinyl chloride at thermal histories which would be destructive to the pure polymers. This fact is not a new revelation but the use of the differential thermal analysis instrument permits quantizing results; thus, a more logical and scientific assessment of vinyl formulations can take place, replacing more laborious techniques currently used.

## APPENDIX

The heat of dehydrohalogenation may be calculated by the expression (9-11):

$$\text{peak area} = \int_{t_1}^{t_2} \Delta T dt = \frac{HM}{g\tau_s} \quad (\text{Eq. 1})$$

$t_1$  = onset temperature of transition,  
 $t_2$  = sample temperature equals reference temperature,  
 $\Delta T$  = differential temperature,

$M$  = mass of the reactive sample,  
 $g$  = constant dependent on the furnace and sample holder geometry,  
 $\tau_s$  = thermal conductivity of the sample.

If the instrument is calibrated with a suitable standard, such as tin whose heat of fusion is 14 cal./Gm., then  $g$  and  $\tau_s$  can be reduced to one constant,  $K$ , the heat transfer coefficient of the system.

$K$  is determined for each thermocouple by means of the following equations which describe the response of the system:

$$\frac{\text{area}}{\text{Gm.}} = \frac{\text{area of fusion transition of tin} \times \text{range setting } (\mu\text{v.})}{\text{wt. of tin, Gm.}} \quad (\text{Eq. 2})$$

$$\frac{\Delta H_f \text{ of tin (cal./Gm.)}}{\text{area/Gm.}} = \frac{\text{cal.}}{\text{area}} = \frac{\text{cal.}}{\text{mm.}^2} = K \quad (\text{Eq. 3})$$

The heats of transitions can thus be determined by the following equation:

$$\Delta H_f = \frac{K \times \text{peak area in mm.}^2 \times \text{range setting } (\mu\text{v.})}{\text{sample wt., Gm.}} \quad (\text{Eq. 4})$$

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# Dissolution of Sodium Salicylate from Tablet Matrices Prepared by Wet Granulation and Direct Compression

By EDWARD MARLOWE\* and RALPH F. SHANGRAW

A quantitative evaluation of dissolution of active ingredients from tablets is discussed. An investigation of filler-binder, lubricant, disintegrating agent, and hardness on the dissolution rate of sodium salicylate from tablet bases was studied by means of a  $4 \times 3 \times 2 \times 2$  factorial experiment and analysis of variance. The utilization of a filler, spray-dried lactose, which required no preliminary granulation, gave significantly faster release rates than granulations prepared with acacia mucilage, starch paste, or ethylcellulose. The presence of a disintegrating agent notably affected the dissolution rate of the active ingredient, especially where wet granulation was employed. The release of sodium salicylate from several bases was a result of the interaction of many variables and was not dependent solely upon the effect of an individual component.

THE EFFECT of formulation and processing factors on the dissolution rate of active ingredients from compressed tablets has been the subject of a number of reports. Wensley (1), using a modification of the Gershberg-Stoll apparatus, investigated the effects of granulating agents and pressure on the dissolution rate of sodium bicarbonate tablets. Kadar and Walker (2) studied the *in vitro* release of sulfathiazole from compressed formulations using a modification of the U.S.P. XV tablet disintegration apparatus. The effects of particle density and neutral ionic and nonionic compounds on the

dissolution rate of slightly soluble acidic drugs were determined by Parrott *et al.* (3). In a later study by the same workers (4) the influences of bases and buffers on rates of dissolution of acidic solids were investigated. Levy (5-7) studied the effect of formulation factors on the dissolution rate of the active ingredient. Included in the factors studied were the agitation intensity, granule size, starch concentration, compression pressure, and lubricants.

With the advent of new machines and materials, a great many tablets formerly prepared by wet granulation can now be manufactured by direct compression. Various direct compression fillers have been evaluated: spray-dried lactose by Günsel and Lachman (8) and by Duvall *et al.* (9), microcrystalline cellulose by Reier and Shangraw (10), amylose by Kwan and Milosovich

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