suggested that product inhibition (including cross-product inhibition) of drug biotransformation processes may be due to an interaction of the inhibitory agents with cytochrome P-450 (8, 14). Specifically, a competition between the hydroxylated metabolite and the drug for binding sites on cytochrome P-450 was suggested (14).

The observation of product inhibition in the elimination of antipyrine is of particular interest because this drug differs from the others studied so far in that it is very hydrophilic and negligibly bound to plasma proteins. The metabolite 4-hydroxyantipyrine may be a potentially useful inhibitor of drug elimination in human drug therapy (analogous to the use of probenecid as an inhibitor of renal excretion of drugs). However, since its biological half-life in humans is very short[7], it may be most useful as an inhibitor of "first-pass" metabolism. This possibility remains to be explored.

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[7] Semilogarithmic plots of antipyrine concentration in plasma and 4-hydroxyantipyrine excretion rate *versus* time after administration of antipyrine to human subjects yield essentially identical half-life values (15), showing thereby that the biological half-life of 4-hydroxyantipyrine is much shorter than that of antipyrine.

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Solid-State Decomposition of *para*-Substituted Salicylic Acids

PAKDEE POTHISIRI and J. T. CARSTENSEN [x]

Abstract □ A series of *para*-substituted salicylic acids, all crystallizing monoclinically and decomposing by decarboxylation, were shown to adhere to Bawn-type kinetics, and the decomposition rate constants were shown to adhere approximately to a Hammett-type relation. The value of the reaction parameter was −8. Both *para*-substituted salicylic and benzoic acids occur as dimers in the crystalline state. The mechanism whereby the latter decomposes is speculated to be intermolecular in the sense that the substituent from one dimer interacts with the carboxyl group of a neighboring dimer. In the same sense of the word, the substituted salicylic acids decompose by an intramolecular mechanism, *i.e.*, within the dimer unit.

Keyphrases □ Salicylic acids, *para*-substituted—decomposition in the solid state, intramolecular mechanism, Bawn kinetics, Hammett relation □ Solid-state decomposition—*para*-substituted salicylic acids, intramolecular mechanism, Bawn kinetics, Hammett relation □ Decomposition—solid state, *para*-substituted salicylic acids, intramolecular mechanism, Bawn kinetics, Hammett relation

The theory of the kinetics of solid-state decomposition, where a solid decomposes into a liquid and a gas, was developed by Bawn (1); experimental data supporting the theory were reported by Carstensen and Musa (2). In this type of reaction, there are (at least) two parallel decomposition paths: (*a*) the solid itself decomposes *via* a first-order decay route with rate constant k_s in reciprocal time units, and (*b*) the compound saturates the liquid decomposition layer and here decomposes in solution with a rate constant k_l in reciprocal time units. It is assumed that the reaction products do not participate actively in the decomposition in any other way than supplying the liquid vehicle in which part of the overall reaction takes place.

BACKGROUND

As long as there is solid present, the fraction decomposed, x, will accelerate exponentially as shown in Fig. 1; as time progresses, there will be an increasing amount of liquid phase and a decreasing amount of solid phase present. At time t_S, the last solid compound disappears and the solubility, S (moles per mole), of the compound in its decomposition product can be determined from the fraction decomposed, x_S, at time t_S. At times later than t_S, the decomposition will be a conventional first-order decomposition with the shape denoted by BC in Fig. 1, so the overall curve (ABC in Fig. 1) will be of the frequently reported sigmoid shape.

One assumption made is the first-order decomposition in the solid phase; this point has been justified both theoretically and ex-

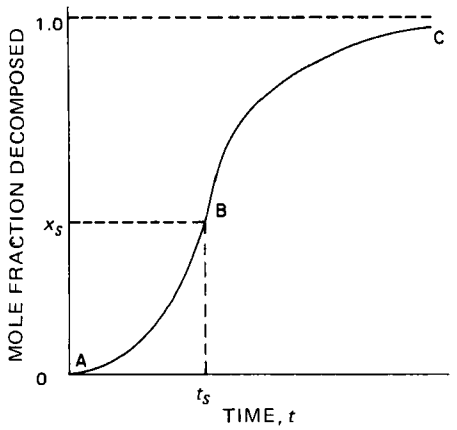

Figure 1—*Typical sigmoid-shaped curve for fraction decomposed in a solid as a function of time, when the solid decomposition produces a gas and a liquid. AB is the acceleratory period where both parent solid and liquid decomposition products are present, and BC is the part of the curve where only the liquid phase is present. The time scale is linear.*

perimentally by the authors (3). The assumption that the liquid reaction product is inert has been justified by consistency checks of the values of k_l obtained from the AB and BC portions of the curve in the case of substituted benzoic acids (2).

For a series of *para*-substituted benzoic acids, Carstensen and Musa (2) showed that the substituent σ-values have to be more negative than −0.3 for the compound to decompose below its melting point. Although the log k_s *versus* σ plot did not give a good linear fit, the correlation coefficient was high (0.9) and the reaction parameter, ρ, was positive. There have been other attempts reported in the literature to tie in reaction rates with substituent σ-values in solid-state reactions. Clark (4–6) found no such effect in a series of malonic acids, and Dorko *et al.* (7, 8) found no systematic correlation in decomposition reactions of tosylates. On the other hand, Meyers *et al.* (9) studied the reaction of benzoic acid derivatives with their salts at elevated temperatures under vacuum and obtained a systematic relation between the reactivities and the substituent σ-values of the compounds.

The aim of the study reported here was to determine whether a chemical substituent effect exists for k_s in a Bawn-type decomposition. A series of *para*-substituted salicylic acids was chosen because they were found experimentally to crystallize in the same crystal system (monoclinic) and they exhibited a clean decarboxylation decomposition without side reactions. These compounds, furthermore, have been studied in solution in quinoline (10, 11); in such solutions, they exhibited a linear free energy relationship for substituents with σ-values of less than +0.3.

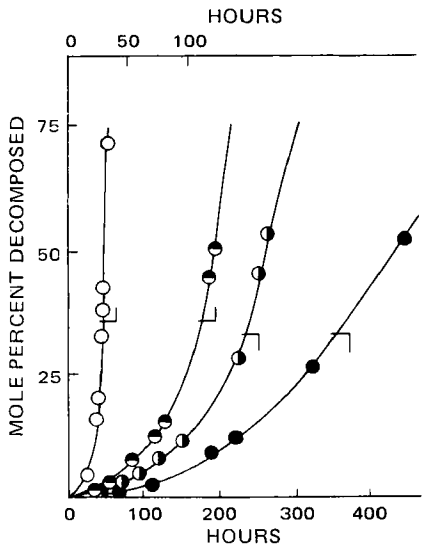

Figure 2—*Typical experimental decomposition curves. The data are* p-*ethoxysalicylic acid at 384°K (●), 399°K (◑), 404°K (◓), and 414°K (○).*

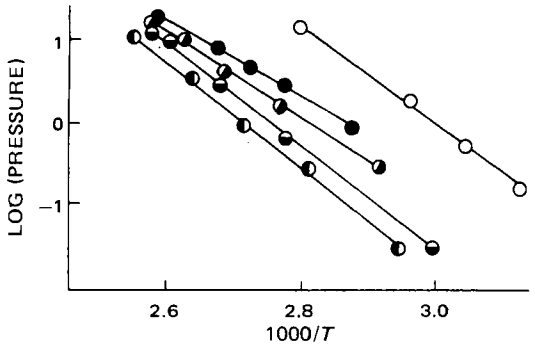

Figure 3—*Vapor pressure curves of five substituted salicylic acids. Key:* ○, p-*amino;* ◒, p-*diethylamino;* ◐, p-*dimethylamino;* ◑, p-*ethoxy; and* ●, p-*hydroxy.*

EXPERIMENTAL

Samples[1] of *p*-dimethylaminosalicylic acid, *p*-diethylaminosalicylic acid, *p*-hydroxysalicylic acid, and *p*-ethoxysalicylic acid were purified by recrystallization from anhydrous methanol. The crystals were reduced by grinding in a porcelain mortar and pestle to a particle size of 8–10 μm as measured by permeamitry[2]. Sample preparation and gas analysis methods were as described elsewhere (2, 3). As in the quoted cases dealing with *para*-substituted benzoic acids, the volatility of the compounds prohibits the use of conventional vacuum setups (12) since they would cause sublimation of the compound from the heated reaction site to the cooler analysis portion of the apparatus. Therefore, the break-seal technique described by Carstensen and Musa (2) was used; sample sizes were 300 mg.

The amount of decomposition was monitored by the number of moles of gas produced. The remaining solid was titrated and the amount of titer lost was shown to equal the number of moles of gas evolved, so the reactions are stoichiometric and of the form: $XC_6H_3(OH)COOH \rightarrow XC_6H_4OH + CO_2$. Since the compounds tested are somewhat volatile at the temperatures used in the study, their vapor pressures were determined as described elsewhere, as were the gas phase decomposition rate constants (2). The value of t_S was determined (to within 15 min) by visual observation of the break-seal tubes in each kinetic run.

The σ-values for one compound, *p*-diethylaminosalicylic acid, is

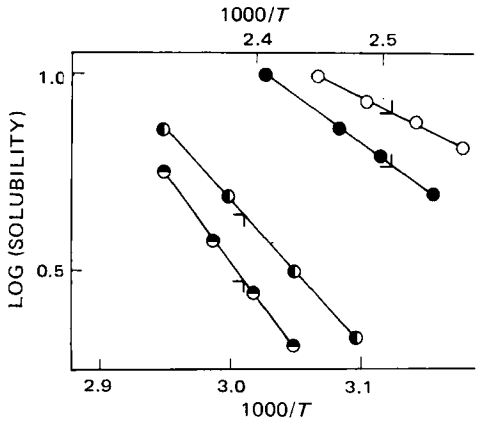

Figure 4—*Solubility–temperature plots of four* para-*substituted salicylic acids. Key:* ◒, *diethylamino;* ◐, *dimethylamino;* ●, *ethoxy; and* ○, *hydroxy.*

[1] Aldrich Chemical Co., Milwaukee, WI 53233

[2] Fisher sub-sieve sizer, Catalog No. 14-311, Instrument Division, Fisher Scientific, Pittsburgh, Pa.

Table I—Substituent σ-Values for Some *para*-Substituents

Substituent X	pKa of XC_6H_4COOH	σ[a]	pKa of $XC_6H_3(OH)COOH$	pKa (H) − pKa (X)
H	4.21	0	2.90[d]	0
OC_2H_5	4.45	−0.24	3.16[b]	−0.26
OH	4.59	−0.37	3.23[b]	−0.33
$N(CH_3)_2$	5.05 (6.01[c])	−0.84 (−1.88)	3.76[b]	−0.86
$N(C_2H_5)_2$	(6.19[c])	(−1.98)	3.84[b]	−0.94

[a] References 14 and 15. [b] Values obtained in this laboratory at 25 ± 0.1°. [c] Reference 16. [d] Reference 17.

unreported in the literature. The pKa value of each compound was determined potentiometrically according to the method of Albert and Sergeant (13).

RESULTS AND DISCUSSION

All of the compounds exhibited decomposition curves of the type shown in Fig. 1; the decomposition curves for *p*-ethoxysalicylic acid are shown in Fig. 2. The results from the vapor pressure determinations are shown in Fig. 3. The linearity gives some assurance (although it does not guarantee) that the compounds do not undergo polymorphic transformation in the temperature range studied. The decomposition rate of the compounds in the gaseous state was of such a magnitude that it would contribute less than 1% of the total decomposition in an ordinary solid run; in the following discussion, it is assumed that vapor phase decomposition can be neglected.

As mentioned, the solubility of the *para*-substituted salicylic acids in their corresponding *meta*-substituted phenols can be determined by removing the break-seal tube at the time of complete

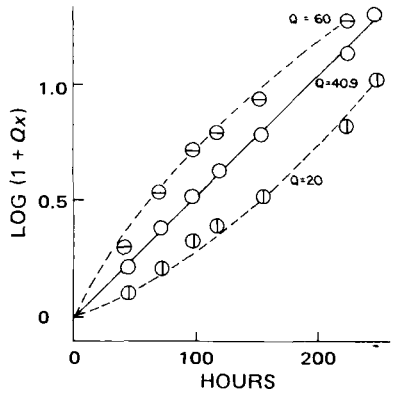

Figure 5—*Plot of ln [1 + Qx] versus time (Eq. 1) for varying values of* Q. *The data relate to the solid-state decomposition of* p-*ethoxysalicylic acid at 399°K.*

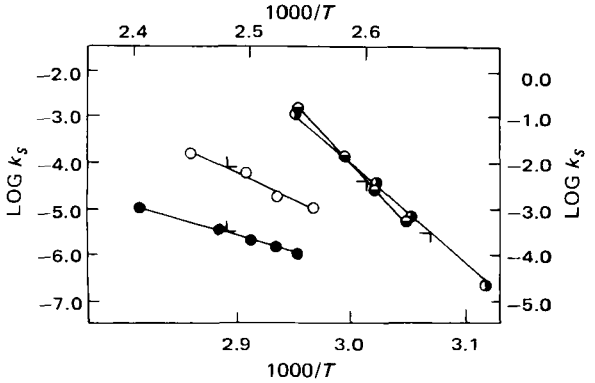

Figure 6—*Temperature dependence of decomposition rate constants in the solid state for* para-*substituted salicylic acids. Key:* ◑, *diethylamino;* ◒, *dimethylamino;* ●, *ethoxy; and* O, *hydroxy.*

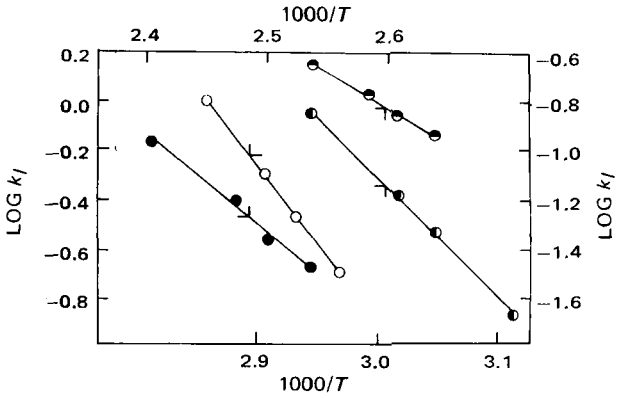

Figure 7—*Temperature dependence of decomposition rate constants in the liquid state for* para-*substituted salicylic acids in their decarboxylated analogs. Key:* ◒, *diethylamino;* ◐, *dimethylamino;* ●, *ethoxy; and* O, *hydroxy.*

liquefaction, t_S, and determining the mole fraction, x_S, decomposed. The solubility is then determined as $S = (1 - x_S)/x_S$ moles per mole. The solubilities are shown in Fig. 4, and the fact that log S is linear in $(1/T)$ is an indication (although no guarantee) that no polymorphic transformation takes place in the temperature range of the kinetic study.

The pKa values determined are shown in Table I, as are a series of reported σ-values for the substituents in question. The last column, denoted pKa (H) − pKa (X), is the difference between the pKa of the unsubstituted salicylic acid and the pKa of the X-substituted salicylic acid. The σ-value for the diethylamino substituent based on the pK value of the diethylaminobenzoic acid (6.19) appears to be of an abnormally high negative value. Since values of pKa (X) − pKa (H) for the salicylic acid series in the case of ethoxy, hydroxyl, and dimethylamino substituents are identical to reported σ-values, the value of pKa (H) − pKa (X) for diethylaminosalicylic acid was used in this study as was the σ-value for the diethylamino substituent.

If a solid decomposes into 1 mole of gas and 1 mole of a liquid decomposition product, then the mole fraction decomposed, x, is given by (1–3, 18, 19):

$$\ln [1 + Qx] = Qk_s t \qquad \text{(Eq. 1)}$$

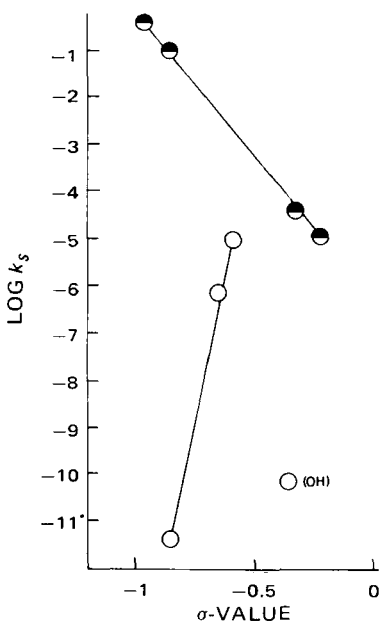

Figure 8—*Hammett-type plot of a series of* para-*substituted salicylic acids (◒) and benzoic acids (O). (The latter are from Ref. 2.)*

Table II—Kinetic Parameter Values for Decomposition of *para*-Substituted Salicylic Acids in the Solid State

Parameter	Substituent			
	OH	OC_2H_5	$N(CH_3)_2$	$N(C_2H_5)_2$
σ	−0.33	−0.25	−0.86	−0.94
log k_s (100°)[a]	−4.45	−4.84	−0.89	0.59
log k_l (100°)[b]	−2.23	−1.27	0.97	0.89
E_a (solid), kcal/mole[a]	52.5 ± 1.7	33.0 ± 0.3	100 ± 3	119 ± 2
E_a' (liquid), kcal/mole[b]	27.1 ± 0.2	19.2 ± 0.8	19.0 ± 0.7	13.2 ± 0.3
log Z (solid)[a], hr^{-1}	26.1	14.4	61.6	73.6
log Z_l (liquid)[b], hr^{-1}	13.6	9.9	12.1	8.6
Melting point, T_m, °K	498.6	426.1	413.1	409.9

[a] $k_s = Ze^{-Ea/RT}$. [b] $k_l = Z_l e^{-Ea'/RT}$.

where:

$$Q = k_l S - k_s S - k_s \qquad \text{(Eq. 2)}$$

Q is found by iteration and is the value which in Eq. 1 imparts linearity to the data. The data in Fig. 5 are data from Fig. 2 plotted in the form of Eq. 1. Knowing Q allows calculation of k_s from the best slope, and then knowing S allows calculation of k_l from Eq. 2. The value of k_l can also be obtained from the part of the decomposition curve beyond the inflection point ($t > t_S$), and k_l values found in the latter fashion agree with the former to within ±25%. Values of k_s and k_l (from Eq. 2) are plotted logarithmically *versus* reciprocal temperature in Figs. 6 and 7; the Arrhenius relationship holds well in both cases.

Gomes (20) reported that there is an inherent difficulty in assigning thermodynamic parameters to data from solid-state reactions. This difficulty is primarily due to the facts that such reactions frequently are dictated and controlled by physical phenomena (*e.g.*, strain and diffusion) and that the solid-state reaction rate constants are not comparable to conventional constants in solution kinetics. In topochemical reactions, for instance, rate constants have dimensions of square centimeters per second where square root laws pertain (21, 22). In contrast, the k_s in this study is of a usual first-order dimension; the data are summarized in Table II. The k_s values[3] are plotted *versus* σ-substituent values in Fig. 8. There appears to be good linearity, and the general correlations imply that the reactions are controlled by chemical factors rather than (or in addition to) physical factors. That the liquid layer may preferentially dissolve a solid at points of strain has been suggested (3) and may minimize the physical factors in a Bawn-type reaction.

As seen in Fig. 8, the trend in a series of *para*-substituted benzoic acids is opposite in sign to that of *para*-substituted salicylic acids. The explanation for this result is sought in the crystallographic arrangement of the two series. Pothisiri (19) described the molecular packing arrangement in crystals of *p*-aminosalicylic acid, *p*-hydroxysalicylic acid, and *p*-aminobenzoic acid (Figs. 9 and 10). *p*-Aminobenzoic acid is built up in dimeric units; hydrogen bonding through the hydrogen of the carboxyl group with the carbonyl oxygen of the neighboring molecule forms links between

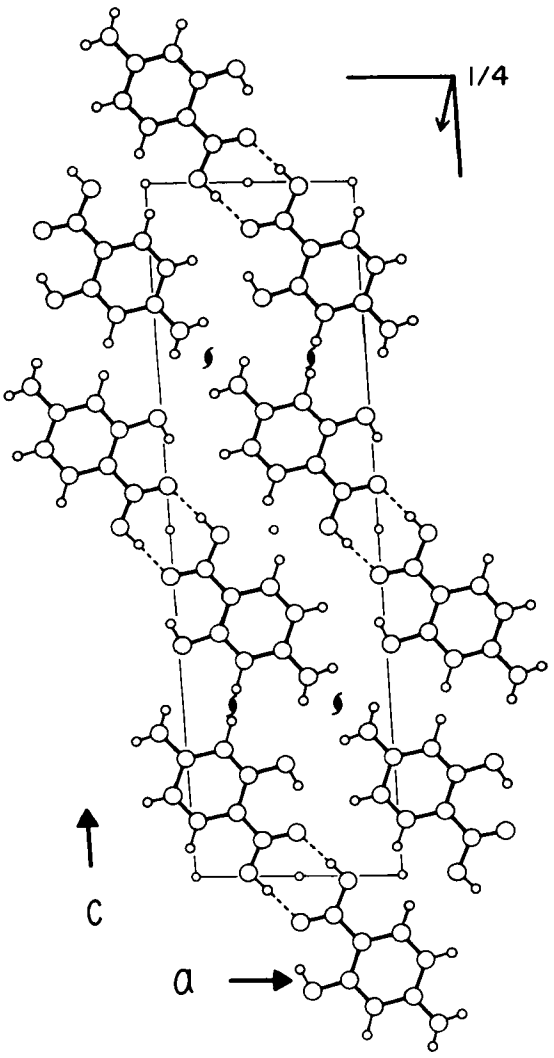

Figure 9—*Packing diagram of* p-*aminosalicylic acid in the [010] projection.*

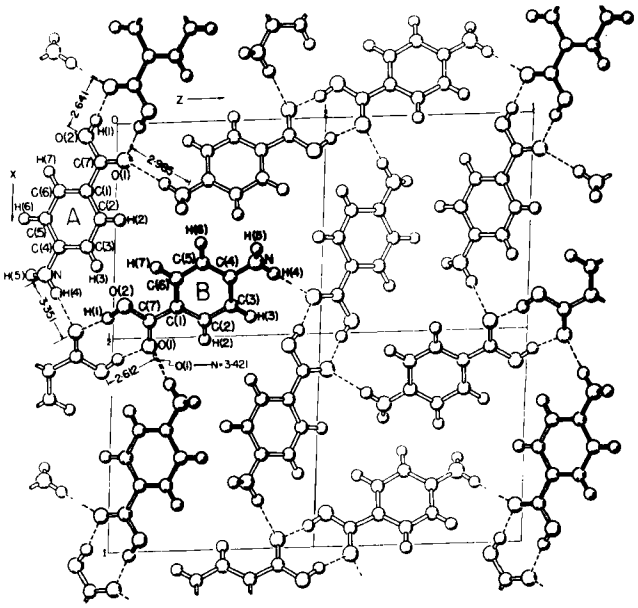

Figure 10—*Packing diagram of* p-*aminobenzoic acid in the [010] projection.*

[3] The k_l values were not plotted in this fashion, since each point corresponds to a different solvent.

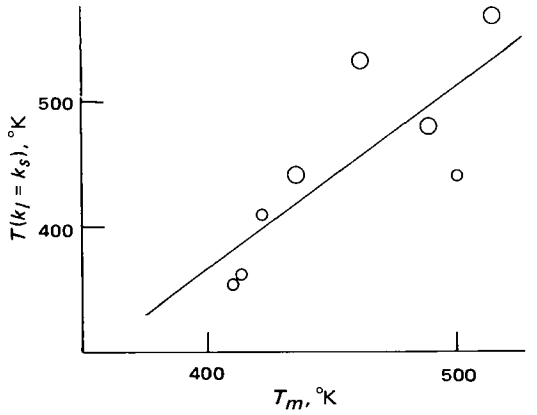

Figure 11—*Plot of the temperature where liquid and solid decomposition rate constants are equal* versus *the melting temperature.*

dimers. The arrangement is such, however, that there is a fairly close proximity (2.985 Å, Fig. 10) between the substituent X of one dimer pair and one carboxyl group of the neighboring pair.

In the case of substituted salicylic acids, however, Fig. 9 shows that the molecular unit is a dimer through hydrogen bonding between carboxyl groups and that a relatively strong intramolecular hydrogen bond exists between the hydroxyl group in the 2-position and the carboxyl oxygen atom. Pothisiri (19) showed that the O(3)—H(2) . . . O(2) distance is 2.610 Å and that there is no hydrogen bonding between the *para*-substituent from one molecule to the carboxyl oxygen of a neighboring molecule (dimer). Therefore, one explanation to the opposite signs of the reaction parameters would be that the *para*-substituted benzoic acid series decomposes *via* an intermolecular mechanism in the sense that there is an interaction between the substituent from one dimer pair with the carboxyl group of a neighboring dimer whereas, in the same sense of the word, compounds in the substituted salicylic series decompose *via* an intramolecular route.

No attempt was made here to seek further substantiation; the proposal should not be construed as a model but rather as a feasible explanation. Several kinetic characteristics (ρ, $\Delta S^{\ddagger}$, and E_a[4]) are of larger magnitude than in solution kinetics. Moreover, some points in the data treatment are not unambiguously resolved; there is, for instance, the possibility of a finite volume of activation which (since the pressure changes during the reaction) could change k_l and k_s as the reaction progresses. Furthermore, although the k_l values from the three-phase part of the curve equal those from the two-phase part[5] to within ±25%, the solution kinetics still could be carbon dioxide dependent, and this may influence the calculated k_s values. The sorting out of such parameters will have to await the results of a systematic kinetic study of *para*-substituted salicylic acids in their corresponding *meta*-substituted phenols at various carbon dioxide pressures.

[4] $\Delta S^{\ddagger}$ is the entropy of activation; it can be calculated from the data in Table II. It is based on a different standard state (moles per mole) than is customary in solution kinetics.

[5] During the latter part of the decomposition, only the liquid and gas phase are present.

The data in Table II allow calculation of the temperatures where k_l and k_s are equal. Such a calculation was performed on the *para*-substituted benzoic acid data reported by Carstensen and Musa (2). When these temperatures are plotted *versus* melting point, a straight line (with correlation coefficient of 0.9) results (Fig. 11). The general significance of this relation (and whether it will extend to other series of compounds) is left undiscussed here.

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