

**Product Studies.**<sup>6</sup>—A 60-ml. solution of 0.0200 *M* in bromotetralone I and 0.0400 *M* in piperidine was allowed to react for 100 hours at 60.0°. The solution was evaporated to dryness. After ether extraction of the residue the filtrate was evaporated to dryness. A 0.230-g. amount of a pale yellow solid was obtained. This represented a 73% yield, calculated as unsaturated ketone. A solution of a portion in acetonitrile gave no precipitate with an acetonitrile solution of silver nitrate, indicating the absence of any unreacted bromotetralone I.<sup>6</sup> The melting point was indefinite, but complete melting occurred lower than 109°. A portion re-

crystallized from methanol gave a white solid, m.p. 112–113°, the endocyclic unsaturated ketone II.<sup>1</sup>

The infrared spectrum of the crude product had  $\nu_{\text{C=O}}$  1662/95 corresponding to the endocyclic unsaturated ketone II<sup>2a</sup>; no other carbonyl peaks or shoulders were present.

The ultraviolet spectrum had considerable absorption in the region 320–340 *mμ*, where the exocyclic unsaturated ketone III absorbs strongly and where the endocyclic unsaturated ketone II has virtually no absorption.<sup>2a</sup> A detailed comparison of the ultraviolet spectrum with those of the pure components II and III showed the product to be a mixture of 87% endocyclic unsaturated ketone II and 13% exocyclic unsaturated ketone III.

(6) Melting points were read with a calibrated thermometer. Ultraviolet absorption spectra were determined with a Cary model 11-MS recording spectrophotometer using reagent grade methanol solutions. Infrared spectra were measured with a Perkin-Elmer model 21 double beam recording instrument employing sodium chloride optics and matched sodium chloride cells with carbon tetrachloride solutions.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SPRAGUE ELECTRIC CO., NORTH ADAMS, MASS.]

## Solvent Effects in the Decomposition of 1,1'-Diphenylazoethane and 2,2'-Azobis-(2-methylpropionitrile)

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Rates of decomposition of 1,1'-diphenylazoethane and 2,2'-azobis-(2-methylpropionitrile) were measured by a very precise technique in several solvents. Significant differences in rate were found, but no simple structural order was evident. A linear relationship was observed between enthalpy and entropy of activation for 2,2'-azobis-(2-methylpropionitrile) in four solvents, but this observation was dismissed as a likely consequence of experimental error. The relationship between errors in rate constants and errors in activation parameters is discussed in detail.

The thermal decomposition of azo compounds in solution is a first-order reaction.<sup>2,3</sup> The rate has been found by many workers to be nearly independent of the medium, while others claim to observe differences in rate in different solvents.

Lewis and Matheson,<sup>4</sup> Overberger, *et al.*,<sup>5</sup> and Arnett<sup>6</sup> offer the conclusion that the rate of decomposition of various azo compounds, including 2,2'-azobis-(2-methylpropionitrile) in each case, is independent of the solvent. The work of Leffler, *et al.*,<sup>7-9</sup> presents an example of a study which led to the conclusion that there are significant rate differences in different solvents. In the decomposition of phenylazotriphenylmethane in several solvents,<sup>7,8</sup> it was concluded that the difference lies in solvation of the reactant molecule through complex formation and that in each case the activation process probably involves desolvation. In the case of *p*-nitrophenylazotris-(*p*-anisyl)-methane<sup>9</sup> it was inferred that some solvents solvate the transition state more than the ground state of the reactant molecule while other solvents function in the opposite manner.

These observations are, of course, limited by experimental errors which are often quite large, and it is recognized that apparent variations in rate may be merely reflections of experimental inaccuracies and that random errors in turn may obscure real rate changes.

The present work represents a study of solvent effects on the rate of the thermal decomposition of two azo compounds, 1,1'-diphenylazoethane and 2,2'-azobis-(2-methylpropionitrile), utilizing a precise measuring technique and striving for accuracy approaching the precision of the technique.

### Experimental

**Rate Measurement.**—Rates of decomposition were determined by measuring nitrogen evolution as a function of time. The measuring apparatus is outlined in Fig. 1. It consists of a reaction cell, gas buret and manometer with a leveling bulb to adjust the mercury in the manometer and buret.

A solution of azo compound was prepared by weight and a known quantity by weight was transferred to the cell. The cell was connected to the measuring system through a standard taper joint and nitrogen was bubbled through the solution, saturating the solution and replacing the air in the measuring system. The nitrogen, which enters the system through stopcock A, leaves through stopcock B, then passes through a bubbler containing a high-boiling liquid to prevent diffusion of air back into the system.

After bubbling N<sub>2</sub> for at least 0.5 hour, stopcock A was closed, the mercury level in the buret was raised to a point near zero and stopcock B was closed. Stopcock C remains open throughout the procedure, its purpose being to aid in detection of leaks and in calibration.

The cell, connected to the measuring system through long capillary tubing and short flexible couplings, was placed in a constant-temperature bath and magnetic stirring was begun. Measurements of buret volume readings and buret (room) temperature were made at constant pressure, using the mercury-leveling bulb, the manometer with a scale and a barometer. Bath temperature varied in a regular cycle by about  $\pm 0.1^\circ$  around the central temperature.

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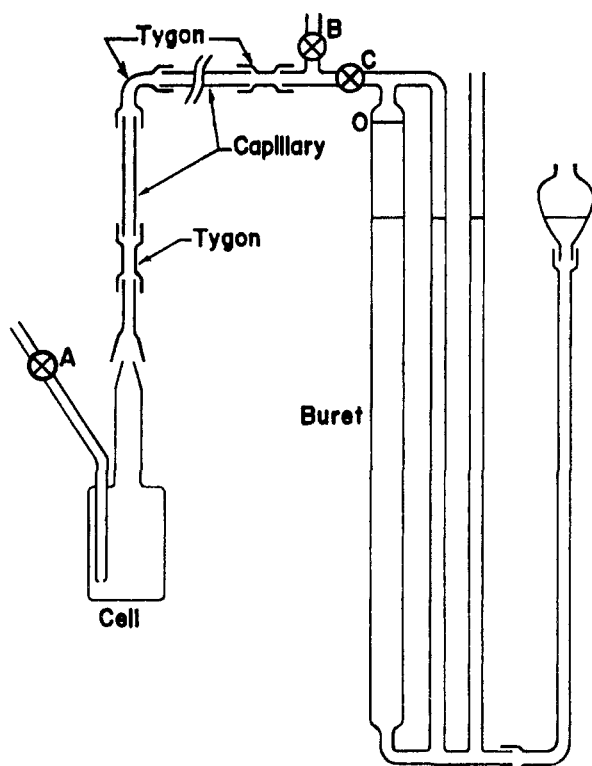


Fig. 1. Apparatus for measuring nitrogen evolution.

The system was treated as consisting of an effective volume  $V_1$  at bath temperature  $T_1$  and an effective volume ( $V_2 + \gamma$ ) at room temperature  $T_2$ , where  $\gamma = \beta B$ ,  $B$  being the buret volume reading and  $\beta$  being a proportionality constant necessitated by the manometer arm in the system, and ( $V_1 + V_2$ ) is the gas volume of the system with the mercury level at  $B = 0$ . The value of  $\beta$  was determined to be 1.228 both by measuring the bore of the manometer arm and by  $P, V, T$  measurements. Applying the perfect gas law, the total number of moles of gas in the system is

$$n = \frac{P}{R} \left[ \frac{V_1}{T_1} + \frac{V_2}{T_2} + \frac{\gamma}{T_2} \right] \quad (1)$$

The increase in the number of moles of gas between two measurements at times  $t = t'$  and  $t = 0$  is

$$\Delta n = n' - n = \frac{P}{RT_2} \left[ \gamma' - \gamma - (\gamma + V_2) \frac{\Delta T}{T_2} \right] \quad (2)$$

where  $\Delta T = T_2' - T_2$ . The term  $(\gamma' - \gamma)$  is the straightforward product of the constant  $\beta$  and the difference between two buret readings while the term  $(\gamma + V_2)\Delta T/T_2$  is a correction factor for variations in room temperature;  $V_2$  can be determined with fair accuracy by  $P, V, T$  measurements with the cell in the constant temperature bath at operating temperature. Any error in  $V_2$  is relatively unimportant. For example, in the apparatus used for the measurements reported here,  $(\gamma' - \gamma)$  is about 50 cc. for a complete run,  $V_2$  is about 20 cc.,  $\gamma$  is nearly zero,  $T_2$  is about 300°K. and a large  $\Delta T$  would be 5°. In this case  $(\gamma + V_2)\Delta T/T_2$  is  $1/3$  cc. or about  $2/3$  of 1% of the total amount of gas evolved. Thus an error of 15% in  $V_2$  creates an error of 0.1% in  $\Delta n$  when room temperature varies by 5° during the course of a run.

Equation 2 is valid only after thermal equilibrium is reached. It is thus necessary to determine an effective value of the buret reading  $B$  at an effective zero time. This is done by plotting values of  $B$  versus time for about the first 0.5 hour after placing the cell in the bath. The plot shows a very rapid increase in  $B$  for about 2 minutes, corresponding primarily to expansion of gas in  $V_1$ , followed by a transition to the slower increase in  $B$  resulting from decomposition of the azo compound which yields one molecule of  $N_2$  for each decomposed azo molecule. It is possible to select from this, by relatively arbitrary extrapolation procedures, an

effective value of  $B$  at an effective zero time which will be sufficiently accurate that the resulting error in rate constant will probably be less than 1%. The accuracy of the technique is tested by following the decomposition reaction to completion (assuming pure azo compound) or by estimating the change in  $B$  due to expansion of gas in  $V_1$  (ignoring or estimating gas solubility variation with temperature and assuming an adequate knowledge of  $V_1$ ). These tests are, however, crude relative to the precision of the measuring technique. The extrapolation procedure is the source of greatest possible error, while lack of purity of the azo compounds represents the second most significant source of error.

Using values of  $\Delta n$  as a function of time and knowing the number of moles of azo compound initially in the cell, the standard first-order kinetic treatment is applied and rate constants are evaluated.

**Azo Compounds.**—Eastman Kodak Co. white label 2,2'-azobis-(2-methylpropionitrile) was recrystallized twice from anhydrous ether; m.p. 101–101.5°. Acetophenone hydrazine<sup>10</sup> was oxidized by the method of Robertson<sup>11</sup> to 1,1'-diphenylazoethane which was twice recrystallized from methanol; m.p. 70–71°.

**Solvents.**—Eastman Kodak Co. *n*-dodecane was distilled, b.p. 97.8° (11 mm.). Union Carbide Chemicals Co. propylene carbonate was distilled, b.p. 94° (4 mm.). Union Carbide Chemicals Co. dibutyl Carbitol (di-*n*-butyl ether of diethylene glycol) was distilled three times, taking a center fraction each time. The fraction used had b.p. 128.3–128.4° (10 mm.). Eastman Kodak Co. white label *N*-methylpropionamide was distilled, b.p. 125.0° (45 mm.), 90–92° (~6 mm.). 1,2-Bis-(benzyloxy)-ethane was distilled, b.p. 147° (0.8 mm.). Eastman Kodak Co. diphenylmethane was distilled, b.p. 129.3–129.5° (11 mm.). Eastman Kodak Co. white label *N*-methyl-*N*-benzylaniline was distilled, b.p. 169–170° (11 mm.). Union Carbide Chemicals Co. butyl Carbitol (mono-*n*-butyl ether of diethylene glycol) was distilled, b.p. 115.5° (11 mm.). Eastman Kodak Co. white label *N,N*-dimethylaniline was distilled, b.p. 77.3–77.9° (10 mm.).

## Results

Rates of decomposition of the azo compounds are listed in Tables I–IV, Table I containing results of measurements on 1,1'-diphenylazoethane while Tables II–IV give results with 2,2'-azobis-(2-methylpropionitrile). The column headed A contains the number of moles of azo compound initially placed in the reaction cell, about 25 cc. of solvent being used in each case, while  $k_1$  is the first-order reaction rate constant.

TABLE I  
DECOMPOSITION OF 1,1'-DIPHENYLAZOETHANE AT 97.30°

Solvent	moles $\times 10^3$	sec. $k_1 \times 10^6$
Dodecane	2.128	3.175
Propylene carbonate	2.168	3.294
Dibutyl Carbitol	2.117	3.351
<i>N</i> -Methylpropionamide	2.349	3.688
<i>N</i> -Methylpropionamide	4.153	3.706
1,2-Bis-(benzyloxy)-ethane	4.362	3.725
1,2-Bis-(benzyloxy)-ethane	2.128	3.740
Diphenylmethane	2.123	3.995
<i>N</i> -Methyl- <i>N</i> -benzylaniline	2.153	4.135

The rate constants were obtained by least-squares treatment of values of  $\ln[A/(A - \Delta n)]$  versus time, limiting the treatment to data obtained between 4 and 60% reaction in all cases. The very early points were eliminated because of a slight deviation from linearity in this range (corresponding to the approach to thermal equilibrium) and

(10) S. G. Cohen, S. J. Groszoz and D. B. Sparrow, *J. Am. Chem. Soc.*, **72**, 3947 (1950).

(11) J. A. Robertson, U. S. Patent 2,520,339, August 29, 1950.

TABLE II  
DECOMPOSITION OF 2,2'-AZOBIS-(2-METHYLPROPIONITRILE)  
AT 66.82°

Solvent	$A_1$ moles $\times 10^3$	$k_1$ sec. <sup>-1</sup> $\times 10^4$
Butyl Carbitol	2.010	2.719
Propylene carbonate	1.990	2.744
Diphenylmethane	1.972	2.891
N-Methylpropionamide	1.997	2.943
N,N-Dimethylaniline	3.269	3.382
N,N-Dimethylaniline	2.181	3.388

TABLE III  
DECOMPOSITION OF 2,2'-AZOBIS-(2-METHYLPROPIONITRILE)  
AT 67.02°

Solvent	$A_1$ moles $\times 10^3$	$k_1$ sec. <sup>-1</sup> $\times 10^4$
Dibutyl Carbitol	2.006	2.442
1,2-Bis-(benzyloxy)-ethane	1.994	3.100
N-Methyl-N-benzylaniline	1.986	3.255
N-Methyl-N-benzylaniline	1.978	3.275
N,N-Dimethylaniline	1.984	3.483

TABLE IV  
DECOMPOSITION OF 2,2'-AZOBIS-(2-METHYLPROPIONITRILE)  
AT 72.23°

Solvent	$A_1$ moles $\times 10^3$	$k_1$ sec. <sup>-1</sup> $\times 10^4$
Propylene carbonate	1.983	5.821
Diphenylmethane	2.001	6.057
N-Methylpropionamide	2.008	6.259
N,N-Dimethylaniline	2.214	6.914

because the large number of points taken in this range would carry inordinate weight in the least squares procedure. The 60% upper limit was established so that the computation would cover the same range for all runs, some of which were terminated at this point.

Probable errors in  $k_1$  were computed and these ranged around 0.1%. Different runs in the same solvent at the same temperature yielded the same value of  $k_1$  within  $\pm 0.4\%$ , independent of concentration. Four examples of this reproducibility are included in the data of Tables I-IV.

The solvents used in this study were chosen to have very low vapor pressures at the operating temperature in an effort to avoid non-random errors which may arise from solvent vapor. This fact, coupled with the extremely small random errors and the excellent reproducibility achieved, leads to the positive conclusion that the rates of decomposition of these azo compounds are dependent on the nature of the solvent.

The solvents are listed in each table in order of increasing rate and it can be seen that the order with 1,1'-diphenylazoethane roughly parallels that with 2,2'-azobis-(2-methylpropionitrile). There is, however, no clear structural basis for the solvent order beyond the fact that rates in aromatic solvents tend to be faster than rates in non-aromatic solvents, the sole exception being N-methylpropionamide which produces a slightly faster rate than diphenylmethane in the decomposition of 2,2'-azobis-(2-methylpropionitrile).

The rates of decomposition of both 1,1'-diphenylazoethane<sup>10</sup> and 2,2'-azobis-(2-methylpropionitrile)<sup>4-6,12</sup> have been studied previously. The

observed rates are not inconsistent with those reported here, but detailed comparison is impossible due to the diversity of measuring conditions.

**Enthalpy-Entropy Relationship.**—By transition-state theory, assuming a sufficiently simple reaction path and a transmission coefficient of unity

$$k_1 = \frac{kT}{h} e^{-\Delta F^\ddagger/RT} = \frac{kT}{h} e^{\Delta S^\ddagger/R} e^{-\Delta H^\ddagger/RT} \quad (3)$$

where  $k_1$  is the first-order rate constant,  $T$  is absolute temperature,  $k$  is the Boltzmann constant,  $h$  is Planck's constant and  $\Delta F^\ddagger$ ,  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  are, respectively, free energy, entropy and enthalpy of activation. Measurements of  $k_1$  at two or more temperatures can be used to obtain a value for  $\Delta H^\ddagger$ , assuming  $\Delta S^\ddagger$  to be independent of temperature; then  $\Delta S^\ddagger$  can be evaluated from the same data, provided that  $\Delta H^\ddagger$  is independent of temperature.

Leffler<sup>13</sup> discussed relationships between enthalpy and entropy observed in organic chemistry, while Leffler, *et al.*,<sup>7-9</sup> have studied the enthalpy-entropy relationship in the thermal decomposition of azo compounds in various solvents.

In the present work, the four solvents used for the decomposition of 2,2'-azobis-(2-methylpropionitrile) at 72.23° were also used at 66.82°. These data were used to compute values of  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for the four solvents. The results are shown in Table V, arranged in order of decreasing  $\Delta H^\ddagger$ .

TABLE V  
DECOMPOSITION OF 2,2'-AZOBIS-(2-METHYLPROPIONITRILE)  
ACTIVATION PARAMETERS

Solvent	$\Delta H^\ddagger$ , kcal./mole	$\Delta S^\ddagger$ , cal./mole-deg.
N-Methylpropionamide	31.86	14.19
Propylene carbonate	31.75	13.73
Diphenylmethane	31.21	12.25
N,N-Dimethylaniline	30.08	9.23

A plot of these values of  $\Delta H^\ddagger$  versus  $\Delta S^\ddagger$  is a straight line of slope 360°. The solvent order in Table V is the same as that of Table IV, except that N-methylpropionamide is removed from its position between two aromatic solvents in Table IV to a position very close to propylene carbonate in Table V. The solvent order with respect to  $\Delta H^\ddagger$  can be explained readily on the basis of complexing and solvation arguments much like those of Leffler, *et al.*,<sup>7-9</sup> but it is first necessary to investigate the possible effects of experimental error.

The relationship between error in measured quantities and error in  $\Delta H^\ddagger$  can be obtained by reference to eq. 3. Regardless of the exact technique used,  $\Delta H^\ddagger$  is computed in principle from two values of the rate constant,  $k_1$  and  $k_1'$ , measured at two temperatures,  $T$  and  $T'$ , giving  $\Delta H^\ddagger$  as

$$\Delta H^\ddagger = R \frac{T'T}{T' - T} \ln \frac{k_1'T}{k_1T'} \quad (4)$$

Errors in the  $T'T/(T' - T)$  term will be typically of the order of 0.1%, negligible relative to the error contributed by  $\ln k_1'T/k_1T'$ . Also, in the ratio

(12) C. E. H. Bawn and S. F. Mellish, *Trans. Faraday Soc.*, **47**, 1216 (1951).

(13) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

$k_1'T/k_1T'$ , the typical error of less than 0.1% in  $T$  need not be considered relative to the usual error of a few per cent. in  $k_1$ . Now if the maximum possible error in  $\Delta H^\ddagger$  is  $\delta$  and the maximum possible fractional error in  $k_1$  (and  $k_1'$ ) is  $\alpha$

$$\Delta H^\ddagger + \delta = R \frac{T'T}{T' - T} \ln \frac{(1 + \alpha)k_1'T}{(1 - \alpha)k_1T'} \quad (5)$$

and

$$\delta = R \frac{T'T}{T' - T} \ln \frac{(1 + \alpha)}{(1 - \alpha)} \quad (6)$$

or, for  $\alpha \ll 1$

$$\delta = 2R \frac{T'T}{T' - T} \alpha \quad (7)$$

Referring again to eq. 3 to relate  $\alpha$  and  $\delta$  to the maximum possible error  $\sigma$  in  $\Delta S^\ddagger$  gives

$$\Delta S^\ddagger + \sigma = (\Delta H^\ddagger + \delta) \left(\frac{1}{T}\right) + R \ln(1 + \alpha) \left(\frac{hk_1}{kT}\right) \quad (8)$$

and

$$\sigma = \delta \left(\frac{1}{T}\right) + R \ln(1 + \alpha) \quad (9)$$

or, for  $\alpha \ll 1$

$$\sigma = \delta \left(\frac{1}{T}\right) + \alpha R = \delta \left[ \frac{1}{T} + \frac{T' - T}{2T'T} \right] \quad (10)$$

It is thus shown that when  $\Delta S^\ddagger$  and  $\Delta H^\ddagger$  are measured for a series of reactions using the same two temperatures  $T$  and  $T'$  throughout the series, the error in  $\Delta S^\ddagger$  is directly proportional to the error in  $\Delta H^\ddagger$ . If measurements of rate contain a sufficient range of errors ('sufficient' defined by the relative effects of  $\delta$  and variation in the true rate constant  $k_1$  in eq. 8), a plot of  $\Delta H^\ddagger$  versus  $\Delta S^\ddagger$  will be a straight line of slope  $2T'T/(3T' - T)$ . Typically,  $2T'T/(3T' - T)$  is approximately unity, and the slope is then  $T$ . This fact is discussed by Lefler<sup>18</sup> for the limiting case that  $\Delta F^\ddagger$  is constant throughout the series of reactions being considered.

When an observed enthalpy-entropy of activation plot presents a straight line of slope  $T$  with each point situated perfectly on the line, this plot is very likely a demonstration of experimental error. Deviations from this straight line of slope  $T$  can result from somewhat different temperature ranges being employed for the various points or from a wide temperature range being used as well as from true variations in rate constants (defined quantitatively by eq. 8) and from certain types of non-random errors.

It may be noted that, while the addition of one or more experimental points of maximum fractional error  $\alpha$  between temperatures  $T$  and  $T'$  may increase one's confidence in the resultant  $\Delta H^\ddagger$ , it also increases the maximum possible error in  $\Delta H^\ddagger$ .

Returning to eq. 7, it is seen that the value of  $\delta$  can be decreased by lowering the temperature of measurement, increasing the temperature range or decreasing  $\alpha$ . An increase in the temperature range, however, generally leads to an increase in the effective value of  $\alpha$ . When a single measuring technique is used over a small range of temperature, systematic (non-random) errors may be nearly the same in all measurements and degree of reproducibility may provide a measure of  $\alpha$  satisfactory for the purpose of estimating  $\delta$ .

In general, however,  $\alpha$  will always be greater than the observed fractional variation in rate constant.

As the temperature range is extended, rate constants change by orders of magnitude, and non-random errors, present in any experiment, can be expected to vary considerably with the great range of times involved in making measurements. If different measuring techniques are necessitated by the great variation in time scales, the nature of systematic errors again becomes an important function of temperature. Some of the systematic errors will be functions of the individual systems under study, and when these are magnified by use of an extended temperature range, the observed reproducibility is grossly inadequate as an estimate of  $\alpha$ .

It must also be recognized that standard statistical analyses used for determining probable errors, generally not very meaningful with a limited amount of data, are completely invalid in the presence of non-random errors.

It must further be emphasized that probable errors have no significance in evaluating the validity of the observed enthalpy-entropy relationship. When plotting several values of  $\Delta H^\ddagger$  versus corresponding values of  $\Delta S^\ddagger$ , some of the points necessarily contain errors greater than the probable error, and it must be assumed that an error approaching the maximum possible error is present somewhere in the series. In addition, the greater is the number of points used, the greater is the expected range of observed error in  $\Delta H^\ddagger$  (i.e., the greater is the probability that any specific error, including an extreme error, is present).

Given the magnitude of the probable error in a single measurement of  $\Delta H^\ddagger$ , it is possible to compute the probability of the existence, in a series of several such measurements, of an error of magnitude equal to or greater than any given value. In principle, this computation can be used to determine the probability that the observed range of  $\Delta H^\ddagger$  values is the result of random errors. This technique of evaluating the validity of the observed variation in  $\Delta H^\ddagger$  should be avoided for two reasons. First, it ignores the possibility of systematic errors and, second, the probability of the presence of an error equal to or greater than any given value is an extremely sensitive function of the probable error in a single measurement, this quantity seldom being available with sufficient accuracy.

A proper technique of evaluation involves assigning a value to  $\alpha$ , computing  $\delta$  from eq. 6 or 7 and comparing the range of experimental  $\Delta H^\ddagger$  values with  $2\delta$  (since  $\delta$  is just the error in the positive direction). Only if the range of  $\Delta H^\ddagger$  values exceeds  $2\delta$  can any validity be assumed in the observed enthalpy-entropy relationship, and only if the range is much greater than  $2\delta$  can any details of the relationship (e.g., linearity) be inferred.

This method of evaluation has been applied to many published examples of linear or approximately linear enthalpy-entropy of activation relationships; no clearly valid case has been discovered. The evaluation is often difficult because discussion of systematic errors usually is omitted and frequently no means is made available even for estimating

TABLE VI

Reaction	$\alpha$	$T'$ , °K.	$T$ , °K.	$2\delta$ , kcal./mole	Obsd. range of $\Delta H^\ddagger$ , kcal./mole
Decompn. of phenylazotriphenylmethane <sup>8</sup>	0.61	348.0	298.3	11.8	4.5
Decarboxyln. of 3-substd. mesitoic acids in 83% $H_2SO_4$ <sup>14</sup>	.18	344.8	333.8	15.1	6.0
Decarboxyln. of picolinic acid in neut. solvents <sup>15</sup>	.052	446.0	437.7	9.7	9.1
Decarboxyln. of picolinic acid in basic solvents <sup>15</sup>	.064	455.2	447.2	12.9	12.3
Solvolysis in 90% aq. acetone of substd. <i>t</i> -cumyl chlorides <sup>16</sup>	.10	328.2	308.2	4.0	3.5
Dehydrn. of $\beta$ -hydroxy ketones in 1 <i>M</i> $H_2SO_4$ <sup>17</sup>	.072	318.2	298.2	2.7	2.7
Rearrang. of allyl $\beta$ -substd. phenyl ethers <sup>18</sup>	.092	473.0	433.0	3.8	3.8
Acid-catalyzed rearrang. of benzhydryl azides <sup>19</sup>	.15	318.2	298.2	5.7	3.3

reproducibility. It is found in such cases, however, that equating the observed range of  $\Delta H^\ddagger$  values with  $2\delta$  leads to a calculated  $\alpha$  which is quite reasonable for the experimental technique employed.

Table VI lists some examples for which published data provide some estimate of reproducibility. This list was limited to cases which use  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  rather than Arrhenius or collision theory parameters. It was assumed along with the original authors in each case that the proper kinetic order was observed and that  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  were independent of temperature. Each value of  $\alpha$  tabulated is equal to or less than the maximum fractional lack of reproducibility which can be computed from the published data. It should be emphasized that this is not a true maximum error, but is necessarily less than the true  $\alpha$ . The values of  $T$  and  $T'$  listed are the temperature extremes employed for that member of the series which yielded the listed  $\alpha$ . In each case the value of  $2\delta$  is at least as great as the observed range of  $\Delta H^\ddagger$ , and this variation can thus reasonably be attributed to experimental error. These studies were chosen only as examples of the difficulty involved in obtaining a clearly valid relationship between en-

thalpy and entropy of activation and their selection as examples implies nothing beyond this fact.

In the present work, the effect of non-random errors was minimized by making very precise measurements over a small temperature range in solvents of low vapor pressure. Reproducibility considerations alone suggest a value of less than 0.008 for  $\alpha$ . Using this value of  $\alpha$  in eq. 7 gives a value for  $2\delta$  of 1.38 kcal./mole. This is only a little less than the 1.78 kcal./mole range of observed  $\Delta H^\ddagger$  values, and non-random errors have not been considered.

On a purely statistical basis, the probable error in rate constants observed in individual runs translates to a probable error of about 0.06 kcal./mole in  $\Delta H^\ddagger$ . As previously described, an evaluation based on this number would lead to the conclusion that the observed linear relationship between enthalpy and entropy was valid, and such an evaluation would be improper.

From considerations based on maximum possible error, it must be concluded that the major part of the observed linear relationship between enthalpy and entropy of activation is very likely the result of experimental error, not only in the present case but in most, if not all, previously published examples of such a relationship. This does not deny the possibility of the existence of such relationships, but rather implies that the positive demonstration of such a phenomenon is extremely difficult due to the inherent nature and magnitude of the experimental errors.

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## Potential Antiradiation Drugs. II. $\beta$ -Aminomercaptans Derived from D-Allose<sup>1,2</sup>

BY LEON GOODMAN AND JAMES E. CHRISTENSEN

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A complex neighboring group approach provided a successful synthesis of methyl 3-amino-2,3-dideoxy-2-mercapto- $\alpha$ -D-allopyranoside hydrochloride (IX). The blocked 3-aminoaltroside (II) afforded, in two steps, the crystalline dithiocarbamoyl mesylate (VI) which, heated in pyridine, cyclized to the thiazoline V, that was reduced to the thiazolidine IV. Compound IV was deblocked and hydrolyzed, *via* the crystalline mercuric salt VIII, to the aminomercapto glycoside IX.

A number of chemical compounds protect living systems against the degradation caused by ionizing

radiation.<sup>3</sup> Cysteine was one of the earliest of such compounds reported.<sup>4</sup> This amino acid possesses a combination of thiol and amine groups

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(2) For a preliminary announcement of a part of this work, see Paper I of this series, J. E. Christensen and L. Goodman, *J. Am. Chem. Soc.*, **82**, 4738 (1960).

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