TABLE V

TYPICAL DATA FOR THE Me_3SiCl–$Me_3SiOSiMe_3$ EQUILIBRIUM AT 25°

m	HCl %	a_1	a_2	A	B	$10^{-12}K$
10	26.72	0.4246	11,000	0.01511	4.674	10.4
12	30.50	.3224	44,500	.08327	4.631	9.7
14	33.80	.2426	152,000	.3385	4.478	9.6
16	36.82	.1821	438,000	1.148	3.992	7.9
18	39.68	.1349	1,130,000	3.540	2.568	8.3
20	42.20	.0988	2,610,000	6.471	0.8255	9.6

The extrapolated values agree well with values calculated from the equations of these authors. There is admittedly some risk of error in such an extrapolation, but the equilibrium constants are relatively insensitive to small changes in HCl activity, and the K's obtained showed no systematic dependence on HCl concentration. Data obtained from a typical series of determinations are shown in Table V.

Calculation of Equilibrium Constants.—Equilibrium constants were calculated from eq. 3

$$K = \left[\frac{B}{A+B}\right] a_2^2 \Big/ \left[\frac{A}{A+B}\right]^2 a_1 = \frac{B[A+B]a_2^2}{[A]^2 a_1} \quad (3)$$

$$\Delta F = -RT \ln K \quad (4)$$

where

A = moles/liter of R_3SiCl
B = moles/liter of $(R_3Si)_2O$
a_1 = activity of H_2O
a_2 = activity of HCl
K = equilibrium constant
ΔF = molal free energy change
m = molality of the HCl

Determination of ΔH for the Me_3SiCl–$(Me_3Si)_2O$ system.—The result of plotting $100 - R \ln K$ linearly against $1/T$ is shown in Fig. 1, where the slope of the curve at 25° gives ΔH = 24,000 cal./mole.

Acknowledgment.—The authors wish to acknowledge the help of Elmer Schultz and Leonard Bruner in carrying out the work.

[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS SCHOOL OF MEDICINE, BALTIMORE 5, MD.]

The Effect of Geminal Substitution Ring Size and Rotamer Distribution on the Intramolecular Nucleophilic Catalysis of the Hydrolysis of Monophenyl Esters of Dibasic Acids and the Solvolysis of the Intermediate Anhydrides

BY THOMAS C. BRUICE[1a] AND UPENDRA K. PANDIT[1b]

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The intramolecular nucleophilic catalysis of ester hydrolysis by the carboxyl group of monoesters of dicarboxylic acids (*i.e.*, monoester → cyclic anhydride → dibasic acid) has been investigated in regard to the kinetic effects of geminal substitution, ring size and conformation of the carbophenoxy and carboxyl groups. α,α-Dimethyl substitution in both the monosuccinate and glutarate esters brings about an almost identical rare enhancement in anhydride formation. In the glutarate monoester β,β-dimethyl substitution is more effective than α,α-dimethyl substitution in increasing the rate of anhydride formation. The increase in rate of anhydride formation brought about by geminal substitution has been explained on the basis of a decrease in unprofitable rotamer distribution in the ground state. When the nucleophilic carboxyl group is held rigidly in an eclipsed position to the carbophenoxy group the expected large rate enhancement in the formation of anhydride is noted. Succinate monoesters form anhydrides 230 times as fast as the corresponding glutarate esters because of a decrease in the effective distance between the reacting groups, whereas the resultant anhydrides have similar solvolysis rate constants. These results have been explained on the basis that the rate-determining step in each case is the initial nucleophilic attack. The various types of geminal substitution decrease the rates of anhydride solvolysis. Since the rate-determining step in the latter reaction is the attack of lyate species, the kinetically negative effect of geminal substitution is ascribed to the steric hindrance to approach of the nucleophile. Though one or two β-substituents increase the rate of glutaric anhydride formation, only β,β-disubstitution hinders anhydride solvolysis. The existence of one bulky substituent in the equatorial position in the cyclic anhydride explains the lack of steric hindrance to the approach of a nucleophile while in the alicyclic ester a single β-substituent can hinder the rotation of reacting groups away from each other and thus influence the rate.

Introduction

The phenomenon of bimolecular nucleophilic catalysis[2] of ester hydrolysis was first recognized by Bender and Turnquest[3] and by Bruice and Schmir[4] in their studies of the catalysis of phenyl acetate(s) hydrolysis by the nitrogen bases imidazole,[3,4] substituted imidazoles[5] and pyridines.[4,5] The phenomenon has since been treated as a special case of nucleophilic displacement at the ester carbonyl group.[6,7] The intramolecular nucleophilic catalysis of the hydrolysis of the ester bond has been investigated by Garrett,[8] Morawetz,[9,10] Bender[11,12] and Bruice[13–16] and co-workers, and has received particular attention because of its apparent similarity to enzymic catalysis.[17]

(1) (a) Department of Chemistry, Cornell University, Ithaca, New York. (b) Postdoctoral Research Fellow, Department of Physiological Chemistry, The Johns Hopkins School of Medicine.

(2) Bimolecular nucleophilic catalysis of ester hydrolysis is that process in which a nucleophile replaces -OR′ from R–CO–OR′ to yield an intermediate whose rate of formation and hydrolysis is greater than the rate of solvolysis of R–CO–OR′.

(3) M. L. Bender and B. W. Turnquest, THIS JOURNAL, **79**, 1656 (1957).

(4) T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957); *Arch. Biochem. & Biophys.*, **83**, 484 (1956).

(5) T. C. Bruice and G. L. Schmir, THIS JOURNAL, **80**, 148 (1958).

(6) T. C. Bruice and R. Lapinski, *ibid.*, **80**, 2265 (1958).

(7) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960).

(8) E. R. Garrett, *ibid.*, **79**, 3401, 5206 (1957).

(9) H. Morawetz and P. E. Zimmering, *J. Phys. Chem.*, **58**, 753 (1954).

(10) H. Morawetz and I. Oreskes, *ibid.*, **80**, 2591 (1958).

(11) M. L. Bender, Y. Chow and F. Chloupek, *ibid.*, **80**, 5380 (1958).

(12) M. L. Bender, F. Chloupek and M. C. Neveu, *ibid.*, **80**, 5384 (1958).

(13) G. L. Schmir and T. C. Bruice, *ibid.*, **80**, 1173 (1958).

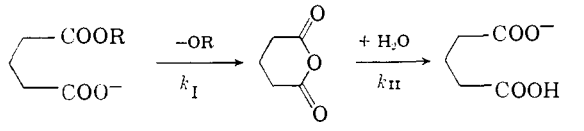
(14) T. C. Bruice and J. M. Sturtevant, *ibid.*, **81**, 2860 (1959).

(15) T. C. Bruice, *ibid.*, **81**, 5444 (1959).

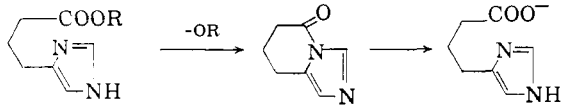
(16) U. K. Pandit and T. C. Bruice, *ibid.*, **82**, 3386 (1960).

(17) H. Morawetz and E. W. Westhead, *J. Polymer Sci.*, **16**, 273 (1955).

The anchimeric participation of the carboxyl group in the hydrolysis of mono-*p*-nitrophenyl glutarate was studied by Morawetz,[17] who found that the rate of *p*-nitrophenol release was in the range of the enzymatic catalysis of phenyl acetate hydrolysis. Even greater rates were observed by Bruice and Sturtevant[14] for the intramolecular nucleophilic catalysis of the hydrolysis of *p*-nitrophenyl γ-(4-imidazolyl)-butyrate.



(1)



Since these catalytic processes involve an initial ring closure (to yield the anhydride and lactam (1), respectively) followed by a hydrolytic ring scission the rates obtained for the over-all process should be highly sensitive to such factors as steric compression, ring size and steric hindrance to lyate and lyate ion attack on the cyclic intermediate. In this paper we describe our findings on the effect of geminal substitution and ring size on the rates of intramolecular catalysis of the hydrolysis of substituted monoesters of a number of dibasic acids. The possible biochemical implications of this study have been pointed out elsewhere.[18]

Results

The rates of hydrolysis of the *p*-bromophenyl esters were determined in 50% (v./v.) dioxane–water at a constant ionic strength of 0.65 *M*, and constant *p*H values between 3 and 7.5 (provided by acetate buffers of constant acetate ion concentration of 0.05 *M*) by following the release of *p*-bromophenol spectrophotometrically at 280 mμ. Rate constants were calculated by the method of Guggenheim,[19] and also from standard curves. The values of the pseudo-first-order rate constants (k_I') calculated by both methods were found to be identical within 5%. When the values of k_I', determined at 30°, and at various hydrogen ion concentrations (assumed here to be the values measured by the glass electrode) are plotted *vs.* *p*H, sigmoid curves are obtained which fit the theoretical dissociation curves for monobasic acids. For the monoglutarate esters the kinetically determined pK_{app}' values were found to be ~ 6.2, while for the monosuccinate esters the values of pK_{app}' were ~ 5.9. The non-identity of the two values plus the fact that the only other weak base present in solution (acetate anion) is at a constant concentration in all experiments establishes the fact that between *p*H 3 and *p*H 7.0 the total rates of hydrolysis of all the glutarate and succinate esters is due to anchimeric participation of the ionized carboxyl group. In Table I are presented the values of k_I', as well as

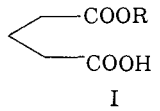
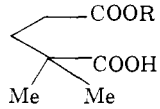
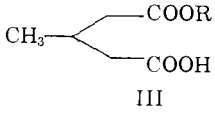
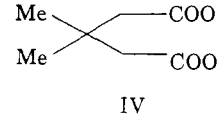
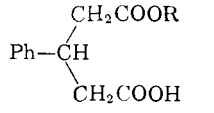
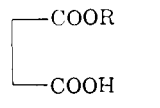
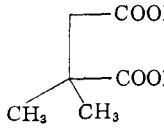
(18) T. C. Bruice and U. K. Pandit, *Proc. Natl. Acad. Sci. (U. S.)*, **46**, 402 (1960).

(19) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

TABLE I

RATE DATA FOR THE HYDROLYSIS OF MONO-*p*-BROMOPHENYL ESTERS OF GLUTARIC AND SUCCINIC ACIDS

CH_3COO^- 0.05 *M*; μ = 0.65 *M* with KCl; solvent 50% (v./v.) dioxane–water; Na 0.05 *M*, *T* = 30°

Ester	*p*H	k'_I, min.$^{-1}$	pK_{app}'	k_I, min.$^{-1}$
 I	4.15	0.000176		
	5.02	.000328		
	5.33	.000648		
	5.65	.000970		
	5.90	.00131		
	6.13	.00189		
	6.45	.00301		
	6.85	.00345		
	7.01	.00360		
	7.00	.00383	6.22	0.00444
 II	5.56	.0025		
	5.80	.0052		
	6.05	.0072		
	6.39	.0094		
	6.60	.0106		
	6.84	.0129		
	6.90	.0135		
	7.00	.0138		
	7.18	.0148	6.20	.016
 III	5.59	.00414		
	5.87	.00575		
	6.35	.0122		
	6.55	.0137		
	6.84	.0153		
	7.00	.0163		
	7.50	.0185	6.23	.0194
 IV	4.76	.0022		
	5.30	.0063		
	5.76	.0123		
	6.34	0431		
	6.51	.0576		
	7.00	.0730		
	7.22	.0740		
	7.45	.0782	6.22	.085
 V	5.22	.0017		
	5.38	.0031		
	5.65	.0040		
	5.94	.0060		
	6.16	.0080		
	6.55	.0114		
	7.05	.0132		
	7.06	.0132	6.08	.0150
 VI	4.71	.088		
	5.10	.184		
	5.59	.418		
	5.84	.544		
	6.10	.662		
	6.35	.740		
	6.60	.836		
	7.00	.940		
	7.05	.954		
	7.18	.983	5.82	1.02
 VII	4.51	.131		
	5.10	.429		
	5.60	1.22		
	6.40	2.33		
	6.64	**2.61**	**5.90**	**3.2**

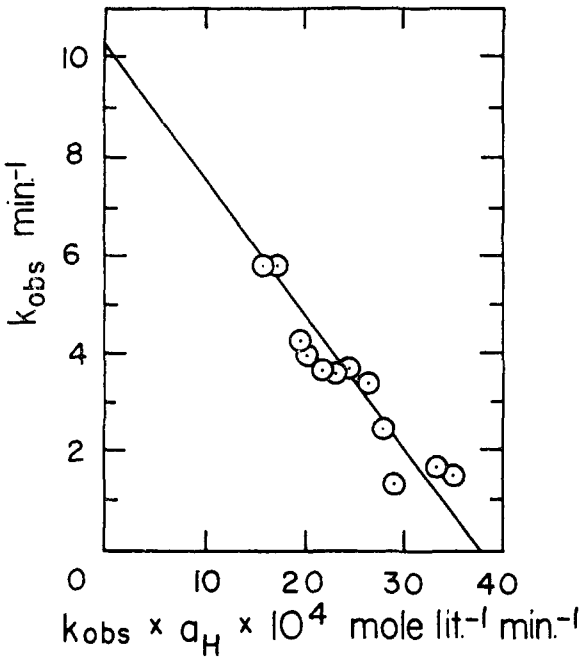


Fig. 1.—Plot of first-order constant against the product of rate constant times hydrogen ion activity for the solvolysis of the *p*-methoxyphenyl ester of *exo*-3,6-endoxo-Δ^4-tetrahydrophthalic acid. The slope is equal to $1/K_{app}$, and the intercept on the rate constant ordinate is the first-order rate for the solvolysis of the ester with participation of the carboxyl anion.

the calculated values for the rates of ester solvolysis with full participation of the carboxyl anion (k_I), (taken as 2× the value of k_I' at the *p*H corresponding to the kinetically determined value of pK_{app}').

The rate of solvolysis of the mono-*p*-bromophenyl ester of *exo*-3,6-endoxo-Δ^4-tetrahydrophthalic acid[20] was so rapid that the release of *p*-bromophenol could not be observed. To obtain data on the extent of carboxyl ion participation it was necessary to study the *p*-methoxy ester and to lower the temperature to 24.5° The difference of 0.5 σ unit between the *p*-bromo and *p*-methoxy groups[21] decreased the rates to manageable values. The *p*-methoxy ester was obtained as its sodium salt (a white amorphous powder) on mixing, under N_2, clear ethereal solutions of sodium *p*-methoxyphenoxide and the 3,6-endoxotetrahydrophthalic anhydride. The free acid could not be obtained because dissolution of the salt in water led to its immediate solvolysis. For the same reason, the sodium salt could not be recrystallized. The identity of the salt rests on the following considerations: (a) *p*-methoxyphenol is liberated by first-order kinetics when the salt is dissolved in glacial acetic acid and added to aqueous buffers, and the quantity of phenol released is quantitative, as determined from a standard curve. (b) The salt reacts rapidly with neutral hydroxylamine to give the corresponding hydroxamic acid. (c) Upon dissolving in H_2O the *p*H immediately moves toward higher values, and then slowly decreases. The increase in *p*H may be associated with the liberation of phenoxide ion and the subsequent slow decrease with the hydrolysis of the intermediate anhydride. The rates of base addition (determined on the *p*H-stat) necessary to maintain constant *p*H during the solvolysis of the intermediate are identical at *p*H 5.5 and *p*H 6.5 to the rate of solvolysis of *exo*-3,6-endoxo-Δ^4-tetrahydrophthalic anhydride. The kinetic observation of the anhydride in the solvolysis of this ester represents the first direct evidence for such an intermediate in the carboxyl anion catalysis of ester hydrolysis. Indirect evidence for anhydride formation in carboxylate catalyzed ester hydrolysis has been previously obtained *via* O^{18} incorporation experiments.[11,22] The phenyl esters of maleic acid and *exo*-3,6-endoxo-Δ^4-tetrahydrophthalic acid are the only esters reported herein in which the rate of anhydride solvolysis is the slow step in the conversion of monoester to the diacid with anchimeric participation of the carboxyl group. For kinetic measurements of X it was necessary to place the ester into solution prior to its addition to the buffered solutions in the spectrophotometer. However, in alcohol or dioxane the sodium salt underwent immediate solvolysis. Clearly an acidic solvent which would repress ionization of the participating carboxyl group was called for. Glacial acetic acid was found to be the solvent of choice. To assure rapid mixing of the acetic acid solution with the buffer, without formation of bubbles and gradients, an aqueous solution rather than 50–50 dioxane–water was employed. At *p*H values above 3.6 k_I' was too large to be determined, and to find k_I and pK_{app}' recourse was made to an Edie type plot[14,15] (Fig. 1). The values of k_I', k_I and pK_{app}' are recorded in Table II. The kinetic procedure employed for the *p*-methoxylphenyl ester of 3,6-endoxo-Δ^4-tetrahydrophthalic acid was also used for the corresponding ester of maleic acid (Table II).

In order that the efficiency of the 3,6-endoxotetrahydrophthalic acid and maleic acid *p*-methoxyphenyl esters could be compared to the glutarate and succinate *p*-bromophenyl esters of Table I, the *p*-methoxyphenyl ester of succinic acid was prepared, and its rate of hydrolysis with carboxyl participation determined in aqueous solution at 24.5° (Table II).

$\alpha,\alpha,\alpha',\alpha'$-Tetramethylsuccinic anhydride and $\alpha,\alpha',\beta,\beta$-tetramethylglutaric anhydride were also prepared, but they were refractive to sodium *p*-bromophenolate in anhydrous ether, so that monoesters of these interesting acids could not be obtained.

Discussion

With the esters studied the over-all efficiency of intramolecular catalysis depends upon the rates of intramolecular nucleophilic attack of the carboxyl anion on the ester bond and the rate of nucleophilic attack of lyate species on the intermediate anhydrides.

In the formation of anhydride electronic effects which decrease pK_{app}' increase the $+\delta$ character of

(20) The structure of the Diels–Alder adduct of furan and maleic anhydride has been shown by Woodward, *et al.* (THIS JOURNAL, **70**, 1161 (1948)) to have the *exo-cis* rather than the *endo-cis* structure.

(21) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

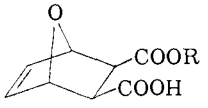
(22) M. L. Bender and M. C. Neveu, THIS JOURNAL, **80**, 5388 (1958).

TABLE II

RATE DATA FOR THE HYDROLYSIS OF MONO-*p*-METHOXYPHENYL ESTERS

$T = 24.5°$, solvent water; μ and acetate ion concentration not controlled

Ester	*p*H	k'_I min.$^{-1}$ × 10^2	k_I	pK_{app}'
Succinate	3.25	0.353		
VIII	3.60	0.618		
	4.00	1.315		
	4.20	1.795		
	4.52	2.66		
	4.88	3.55		
	5.30	4.14		
	6.50	4.21		
	6.92	4.60	4.5	4.34
Maleate	2.05	32.7		
IX	2.10	43.8		
	2.15	37.4		
	2.56	89.9		
	2.60	99.0		
	2.65	92.1		
	3.06	129.3		
	3.15	149.8		
	3.25	158.0	200	2.68
	2.66	152		
	2.69	167		
	2.69	138		
	2.94	244		
	3.11	340		
	3.18	370		
	3.19	358		
	3.22	365		
	3.29	396		
	3.32	411		
	3.52	573		
	3.56	576	1030	3.45



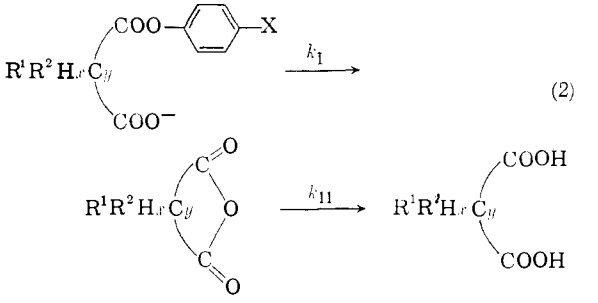
X

TABLE III

RATE OF SOLVOLYSIS (k_{II}) OF ANHYDRIDES AT *p*H 6.5 IN 28.5% ETHANOL–WATER V./V., μ = 0.65 *M*

Anhydride	k_{II}, min.$^{-1}$	*T*, °C.
Glutaric	0.23	35
α,α-Dimethylglutaric	.076	35
β-Methylglutaric	.14	35
β,β-Dimethylglutaric	.017	35
β-Phenylglutaric	.32	35
Succinic	.34	35
α,α-Dimethylsuccinic	.21	35
$\alpha,\alpha,\alpha',\alpha'$-Tetramethylsuccinic	.010	35
3,6-Endoxo-Δ^4-tetrahydrophthalic	1.2	35
Succinic	0.095	20
Maleic	0.739	20

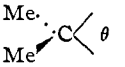
the ester bond undergoing attack. Thus, while the nucleophilicity of the carboxyl anion decreases, the susceptibility of the bond to nucleophilic attack increases. Because the larger alterations in pK_{app}' occur with the esters derived from symmetrical anhydrides (glutarate *vs.* succinate *vs.* 3,6-endoxo-Δ^4-tetrahydrophthalate *vs.* maleate) where the electron density at the ester and carboxyl groups should be equally affected, we may consider the difference in rates of anhydride formation to be due to steric effects only. However, in anhydride solvolysis the rate of nucleophilic attack will be controlled both by the $\delta(+)$ character of the anhydride carbonyl groups and the various steric influences of the substituents. As we shall see these two effects may be easily separated.



(2)

The stereochemical problems dealt with in this study may be separated into the influence of ring size and geminal substitution on k_I and k_{II}. The relative stabilities of five- and six-membered rings with exocyclic double bonds has been treated by Brown and co-workers, resulting in the formulation of the well-known Brown–Brewster–Shechter rule.[23,24]

The enhancement of ring closure reactions and retardation of ring opening reactions by geminal substitution, or indeed alkyl substitution in general, is a well-known phenomenon. Earlier workers assumed, after the suggestion made by Thorpe and Ingold,[25–28] that the geminal substitution effect was due to a decrease in bond angle θ



(3)

brought about by no-bond interaction of the geminal groups (Thorpe–Ingold effect). This hypothesis, however, no longer appears to be in vogue, though recently Searles[29] has presented evidence that appears to indicate that a bond angle deformation occurs in the 2-oxaspirane system upon geminal substitution.

The kinetic effect of geminal substitution can be of the order of 10^4–10^5 for *gem*-diphenyl and *gem*-diisopropyl substitution.[30] Recently, in an investigation of the solvolysis of five-membered cyclic sultones, Bordwell and co-workers[31] proposed that the stabilizing effect on ring structure, by geminal substituents, was due to a decreased ability of the departing atoms to move away from each other in the transition state. Though only sultones were investigated the theoretical considerations brought to bear were intended to be general.

In Table IV are presented the relative rates of ring closure for the esters (k_I/k_1 glutarate) and the

(23) H. C. Brown, J. H. Brewster and H. Shechter, THIS JOURNAL, **76**, 467 (1954).

(24) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(25) R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915).

(26) C. K. Ingold, *ibid.*, **119**, 305, 951 (1921).

(27) G. A. R. Kon, A. Stevenson and J. F. Thorpe, *ibid.*, **121**, 650 (1922).

(28) C. K. Ingold, E. W. Lanfear and J. F. Thorpe, *ibid.*, **123**, 3140 (1923).

(29) S. Searles, paper 100 presented to the Organic Division, A.C.S. Meeting, Boston, Mass., 1959.

(30) R. F. Brown and Norman van Gulick, *J. Org. Chem.*, **21**, 1046 (1956).

(31) F. G. Bordwell, C. E. Osborn and R. D. Chapman, THIS JOURNAL, **81**, 2698 (1959).

TABLE IV

RELATIVE RATES OF ANHYDRIDE FORMATION (FROM MONOESTERS ANION) AND SOLVOLYSIS

	Acid	Relative rate of ester solvolysis k_I/k_I glutarate	Relative rate of anhydride solvolysis $(k_{II}/k_{II}$ glutarate$)^{-1}$
I	Glutarate	1.0	1.0
II	α,α-Dimethylglutaric	3.64	4.3
III	β-Methyl-	4.41	1.7
IV	β,β-Dimethyl-	19.3	13.8
V	β-Phenyl-	3.38	0.72
VI	Succinate	232	0.684
VII	α,α-Dimethylsuccinic	728	1.1
VIII	α,α,α′,α′-Tetramethyl-	.....	23.7
IX	Maleate	10,300	0.089
X	3,6-Endoxo-Δ⁴ tetrahydrophthalate	53,100	0.19

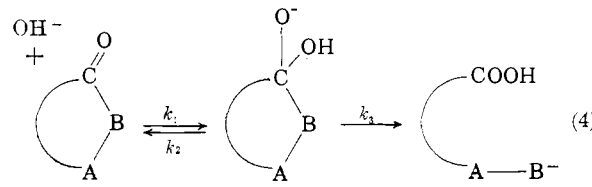
solvolysis of the intermediate anhydrides (k_{II}/k_{II} glutarate)$^{-1}$. Four obvious conclusions may be drawn from inspection of the data of Table IV: (a) *The formation of a five-vs. a six-membered ring has a large effect on the rate of ring closure (compare relative rates for a simple glutarate and succinate esters).* (b) *The rate of ring opening is only slightly affected by ring size (compare k_{II} for glutaric and succinic anhydrides).* (c) *Geminal substitution increases the rates of ring closure and decreases the rates of ring opening. The magnitude of the two effects is greatest for β-geminal substitution.* (d) *Complete restriction of rotation of the reacting carboxyl and carbophenoxy groups away from each other has a profound rate enhancement effect on anhydride formation, but does not decrease the rate of anhydride solvolysis (compare glutarate ester and anhydride with the ester and anhydride of 3,6-endoxo-Δ⁴-tetrahydrophthalic acid).*

The Effect of Ring Size on Anhydride Formation and Solvolysis.—Glutaric and succinic anhydrides solvolyze at comparable rates (the slight difference in rate constants being due to electronic factors; see discussion on geminal substitution) and, therefore, in this instance the Brown–Brewster–Shechter rule is not followed. This, however, is not the case for other cyclic acyl systems (Table V). The mechanism of the hydrolysis of a cyclic acyl compound presumably resembles that accepted for ester hydrolysis.[32]

TABLE V

RELATIVE RATES FOR SOLVOLYSIS OF FIVE- AND SIX-MEMBERED CYCLIC ACYL DERIVATIVES

	k_{six}/k_{five}	Ref.
Lactones	173 (H_3^+O)	23
	23, 37 (OH^-)	23, 32a
Thiolactones	152 (H_3^+O)	33
Lactam	7 (OH^-)	34
N-Methylimide	12 (OH^-)	35
Anhydride	0.7 (pH 6.5)	This study
	1.3 (OH^-)	36



(4)

Assuming a steady state in the tetrahedral intermediate

$$k_{II} = \frac{k_1 k_3}{k_2 + k_3} \text{ where } \alpha = \frac{k_2}{k_3} \qquad (5)$$

It follows that the ratio of the over-all rates of solvolysis of six (k_{II}) and five (k_{II}') membered cyclic acyl derivatives is

$$\frac{k_{II}}{k_{II}'} = \frac{k_1(\alpha' + 1)}{k_1'(\alpha + 1)} \qquad (6)$$

If $k_1 = k_1'$ then the minimum value of $\alpha' \cong k_{II}/k_{II}'$. Inspection of Table V reveals that k_{II}/k_{II}' may be as great as 100–200. However, since the upper limit of α for OH^- or H_2O attack on the ester or anhydride bond has been found to be ~ 0.2 by the O^{18} exchange method of Bender,[37] it follows that relative rate ratios much above 1.0 can only be explained *via* differences in k_1 when either OH^- or H_2O are the nucleophilic agents.

The relative values of the rate constants for the solvolysis of corresponding five- and six-membered cyclic acyl derivatives is perhaps best explained *via* the hybridization, in the transition state, of the carbonyl group undergoing attack. In those instances where the rates are comparable, as in anhydride solvolysis, it is proposed that in the transition state the carbonyl group undergoing attack is mostly in a state of sp^2 hybridization, whereas for those systems in which the six-membered cyclic acyl compound solvolyzes faster than the five it is proposed that the carbonyl group undergoing nucleophilic attack has more sp^3 character. For those six-membered cyclic acyl compounds in which the transition state resembles more closely the tetrahedral intermediate (an sp^3 hybridized C=O) additional nobond interaction would not be involved since all bonds should be staggered. However, for the corresponding five-membered ring compounds the leaving and entering groups would be eclipsed with the neighboring methylene hydrogens (Fig. 2). Since the nobond interaction of neighboring hydrogens in ethane amounts to ~ 1 kcal./mole[38] the above considerations serve to explain the maximum 1–2 kcal./mole difference in ΔF^* for the solvolysis of the corresponding five- and six-membered cyclic acyl derivatives.

In the ring closure reaction the succinate ester undergoes cyclization at a rate 230 times as great as the glutarate ester because of the greater proximity of the reacting groups. The ratio of k_I/k_I' of 230 for this process indicates that the nucleophilic

(32) M. L. Bender, *Chem. Revs.*, **60**, 53 (1960).

(32a) R. Huisgen, *et al.*, *Angew. Chem.*, **69**, 345 (1957); C. W. Matuszak and H. Shechter, Abstracts of 132nd A.C.S. Meeting, New York, N. Y., September, 1957, p. 12P.

(33) E. Schjanberg, *Ber.*, **75**, 468 (1942).

(34) M. Gordon, Thesis, Manchester, 1950.

(35) H. K. Hall, Jr., M. K. Brandt and R. M. Mason, THIS JOURNAL, **80**, 6420 (1958). The rate ratio of 107 for imide hydrolysis employed for illustrative purposes in the formulation of the Brown–Brewster–Shechter rule[23] from data of S. S. G. Sircar, *J. Chem. Soc.*, 600, 1252 (1927), did not take into account the kinetic effect of the ionization of the imide; see J. T. Edwards and K. A. Terry, *ibid.*, 3527 (1957).

(36) J. Koskikallio, *Ann. Acad. Sci. Fennicae, Ser. A*, No. 57 (1954).

(37) See, for example, M. L. Bender, *et al.*, THIS JOURNAL, **78**, 319 (1956).

(38) K. S. Pitzer, *Disc. Faraday Soc.*, **10**, 66 (1951).

attack of the carboxyl anion is associated with the most important transition state.

In order for the glutarate ester to solvolyze with anchimeric participation of the carboxylate ion at a rate equal to that of the succinate ester, a loss of 10 e.u. (at constant $\Delta H^{\pm}$) would be required for freezing the extra bond of the glutarate ester in the transition state. For the succinate ester to solvolyze with participation at the rate of the ester of 3,6-endoxo-Δ^4-tetrahydrophthalic acid again 10 e.u. would have to be lost in freezing out the free rotation of the HC–CH bond of the succinate ester. A value of 10 e.u. per bond is far in excess of the value of 2 e.u. calculated by Pitzer[39] for the entropy of internal rotation about a single bond. However, it should be noted that the formation of cyclopentane from *n*-pentane is favored by $\sim$ 8 e.u. as compared to the formation of cyclohexane from *n*-hexane (25°, gas phase.)[40]

The Effect of Geminal Substitution on Anhydride Formation and Solvolysis.—The observation of the geminal effect in the solvolysis of the anhydride cannot be explained by employing Bordwell's[31] concept of steric hindrance to ring opening, since only the rate of nucleophilic attack (k_1) can be kinetically important in anhydride solvolysis above (see). Similarly, neither does the older Thorpe-Ingold hypothesis serve here for identical reasons. The most logical explanation of the geminal effect would appear to be: (*1*) *The ring closure reaction proceeds at a greater rate on geminal (or alkyl) substitution because of the resultant decrease in unprofitable rotamer distribution.* (2) *The negative geminal effect on ring opening is due to steric hindrance to the approach of lyate species to the anhydride carbonyl group.*

The influence of alkyl substituents on the rotamer distribution of alkyl substituted succinic acids has been known for a long time.[41] Thus, in succinic acid steric hindrance and charge repulsion make the *trans* configuration of the carboxyl groups the more stable one. The introduction of alkyl groups decreases the stability of the *trans* configuration relative to the *cis* because of no-bond repulsion between the alkyl and carboxyl groups. For succinic acid the introduction of alkyl groups in both the α- and α'-position markedly increases the second dissociation and decreases the first dissociation constant. The effect is maximized when both the α- and α'-positions are geminally substituted.[42] Much the same may be said for glutaric acid, and Le Moal[43a] employing the Barton equation[43b] has calculated the decrease in carboxyl group interdistance as a function of geminal substitution in a series of glutaric acids; however, he did not study the substitution patterns employed in this study.

It is proposed that the increase in rate of anhydride formation accompanying geminal substitution is due to a decrease in the probability of the unprofitable rotamer distributions in which the reacting groups have rotated away from each other. For the monoester of 3,6-endoxo-Δ^4-tetrahydrophthalic acid the ester and carboxyl group are fixed in an eclipsed conformation and the participation rate is increased over 200 times that for the nonsubstituted succinate.

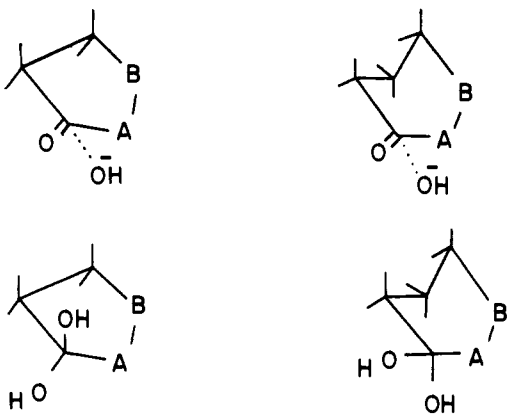


Fig. 2.

For anhydrides with the same steric demands, the rate of solvolysis should be related to the K_{app}' of the monoesters by the usual form of a linear free energy equation.[44]

$$\log \frac{k_{II}}{k_0} = E \log \frac{K_a'}{K_0'} \qquad (7)$$

Steric hindrance to approach of lyate ions and molecules will decrease the log k/k_0 values by an amount which we may call S.

$$\log (k_{II}/k_0) = \log (k_{II}/k_0) - S \qquad (8)$$
steric hindrance no steric hindrance

This leads to the expression

$$\log \frac{k_{II}}{k_0} = E \log \frac{K_a'}{K_0'} - S \qquad (9)$$

In Fig. 3 are plotted the values of log k/k_0 *vs.* log K_{app}'/K_0' employing the k_{II} for succinic anhydride and the K_{app}' for mono-*p*-bromophenyl and *p*-methoxyphenyl succinates as references. It may be noted that a line may be drawn through the points (Fig. 3) for glutaric, β-phenylglutaric, succinic, *exo*-3,6-endoxo-Δ^4-tetrahydrophthalic and maleic anhydrides. This line defines E (E = 0.63) and the negative deviations from the line with slope E are S. The proposed steric effect of the substituent groups may be then discussed in terms of the values of S (Table VI) as calculated from Fig. 3.

Inspection of Table VI reveals that the differences in the rates of solvolysis of glutaric, succinic and maleic anhydrides are attributable to electronic effects only. That β,β-geminal substitution brings about a greater enhancement in rate of formation of glutaric anhydride than does α,α-geminal substitution is to be expected from inspection of Stuart-Brieglieb models since this configuration affords maximum steric repulsion to the rotation of the carboxyl and ester groups away from each other.

(39) K. S. Pitzer, "Quantum Chemistry," Prentice-Hall, Inc., New York, N. Y., 1953.

(40) K. S. Pitzer, *Chem. Revs.*, **27**, 45 (1940); J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2487 (1947); C. W. Beckett, K. S. Pitzer and R. Spitzer, *ibid.*, **69**, 2490 (1947).

(41) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, N. Y., p. 227.

(42) R. Gane and C. K. Ingold, *J. Chem. Soc.*, 2153 (1931).

(43) (a) H. Le Moal, *Bull. soc. chim. France*, 418 (1956); see also N. L. Phalnikar and B. V. Bhide, *J. Univ. Bombay*, **10**, 147 (1941). (b) D. H. R. Barton, *Nature*, **160**, 752 (1947).

(44) As employed, for instance, by R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapt. 13.

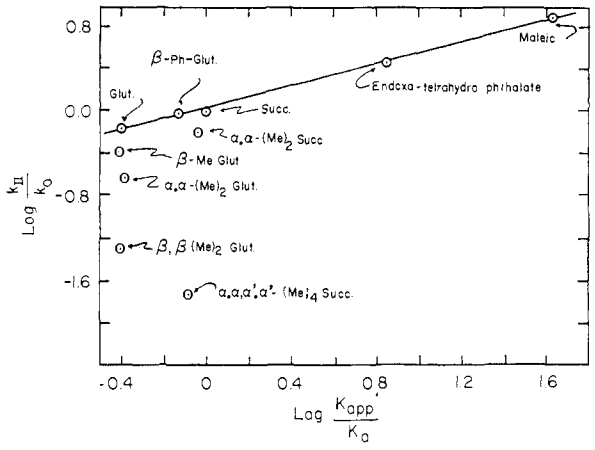
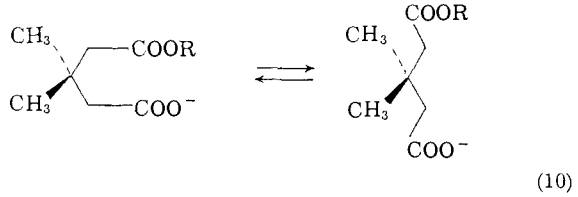
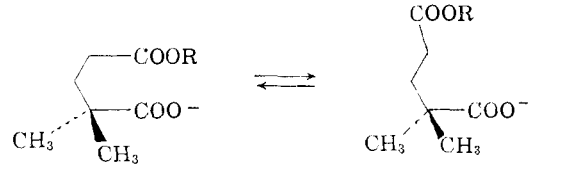


Fig. 3.—Plot of log relative rate of anhydride solvolysis at *p*H 6.5 *vs.* log relative acid dissociation constants of the corresponding monoesters. Succinic anhydride and monosuccinate esters employed as references.

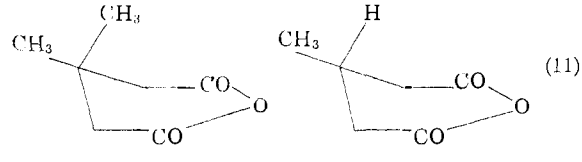
The restriction of rotamer distribution by one β-methyl substituent is apparently similar to that for an α,α-*gem*-dimethyl substitution in the glutarate series (Table IV).



(10)



From inspection of Tables III and IV, it may be seen that the β-methyl or β-phenyl groups have relatively little or no effect on the rate of anhydride solvolysis, but do have a rate-accelerating effect on ring closure. This observation is easily explained on the basis that one β-substituent should hinder rotation of the carbophenoxy and carboxyl anion groups away from each other in the alicyclic ester, but in the cyclic anhydride a single β-substituent would be expected to occupy, in the main, an equatorial position, which would not afford F-strain in the formation of the transition state for anhydride opening.



(11)

Additional support for the hypothesis that the retardation effect of geminal substitution on anhydride hydrolysis is due to F-strain comes from the observations on the rates of reactions of primary and secondary amines with α-N-carboxy amino acid anhydrides.[45] Alkyl substitution in the ring was found to retard nucleophilic attack on the anhydride and the extent of retardation for any given ring substitution was directly relatable to the steric requirements of the alkyl groups on the attacking amine. Though geminal substitution was not studied it was found that a single isopropyl group retarded the rate of nucleophilic attack by isopropylamine, as compared to methylamine, by many orders of magnitude.

TABLE VI

STERIC PARAMETERS (S) FOR THE HINDRANCE OF ANHYDRIDE SOLVOLYSIS

Anhydride	S
Glutaric	0
Succinic	0
Maleic	0
exo-3,6-Endoxo-Δ⁴-tetrahydrophthalic	0
β-Phenylglutaric	0
β-Methylglutaric	0.1
α,α-Dimethylglutaric	0.45
β,β-Dimethylglutaric	1.13
α,α-Dimethylsuccinic	0.21
α,α,α',α'-Tetramethylsuccinic	1.40[a]

[a] $pK_0' - pK_a'$ for the corresponding ester assumed to be twice that of the α,α-dimethyl ester.

Experimental

Dicarboxylic Acids and Anhydrides.—Glutaric, succinic and β,β-dimethylglutaric anhydrides and α,α-dimethylsuccinic and glutaric acids were obtained commercially.[46] β-Methylglutaric, β-phenylglutaric and tetramethylsuccinic acids were prepared by literature procedures.[47-49] 3,6-Endoxo-Δ⁴-tetrahydrophthalic anhydride was obtained by the method of Diels and Alder.[20,50]

The free acids were converted to anhydrides by treatment with acetyl chloride and purified by recrystallization from benzene–ether or chloroform–ether mixtures. The melting points were found to agree with the literature values.

Substituted monophenyl esters were prepared by adding, with constant stirring under nitrogen, a solution of the appropriate sodium phenoxide (prepared by treating 0.01 mole sodium shot with 0.01 mole of phenol under N_2 in 50 ml. of ether) to an ether or ether–benzene solution of the anhydride. Stirring was generally continued for 12 hr. when the gelatinous sodium salt was collected and washed with ether. The sodium salt of the monoester was then dissolved in cold water and the free ester precipitated by addition of 1 *N* HCl. The ester was extracted from the aqueous solution and the ether extract dried over Na_2SO_4. After filtering and evaporation of the ether solvent the residual ester was recrystallized (when possible) several times from benzene–petroleum ether.

p-Bromophenyl ester of succinic acid, m.p. 125–127°. *Anal.* Calcd. for $C_{10}H_9O_4Br$: C, 43.98; H, 3.29; Br, 29.30. Found: C, 44.26; H, 3.48; Br, 29.49.

p-Bromophenyl ester of glutaric acid, m.p. 101–102°. *Anal.* Calcd. for $C_{11}H_{11}O_4Br$: C, 46.00; H, 3.84; Br, 27.89. Found: C, 46.01; H, 3.96; Br, 28.01.

p-Bromophenyl ester of β-methylglutaric acid, m.p. 72.5–73.5. *Anal.* Calcd. for $C_{12}H_{13}O_4Br$: C, 47.82; H, 4.32; Br, 26.59. Found: C, 47.94; H, 4.34; Br, 26.91.

p-Methoxyphenyl ester of maleic acid, m.p. 104–105°. *Anal.* Calcd. for $C_{11}H_{10}O_5$: C, 59.48; H, 4.55. Found: C, 59.64; H, 4.28.

(45) D. G. H. Ballard and C. H. Bamford, *J. Chem. Soc.*, 355 (1958).

(46) K and K Laboratories, 177-10 93rd St., Jamaica, N. Y.

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(50) O. Diels and K. Alder, *Ber.*, **62**, 554 (1929).

p-Methoxyphenyl ester of succinic acid, m.p. 117–118°. *Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.98; H, 5.36. Found: C, 59.10; H, 5.52.

In view of the extreme tendency of the maleic ester to lose *p*-methoxyphenol, the sample was dried at room temperature and 2 mm. over phosphorus pentoxide for 12 hours. The ester released *p*-methoxyphenol quantitatively upon solvolysis.

The *p*-bromophenyl esters of the *gem*-dimethylsuccinic and glutaric acids were obtained as oils which did not crystallize on long standing. The esters of α,α- and β,β-dimethylglutaric acids were identified through their conversion to the known acid anilides, m.p. 128–130°[51] and 146–147°,[52] respectively. The monoesters of α,α-dimethylsuccinic acid and β-phenylglutaric acid were converted to their anilides in the usual manner.

Monoanilide of α,α-dimethylsuccinic acid, m.p. 185–186°, *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.15; H, 6.58; N, 6.34. Found: C, 65.38; H, 6.85; N, 6.59.

Monoanilide of β-phenylglutaric acid, m.p. 168°. *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.07; H, 5.99; N, 4.95. Found: C, 72.20; H, 6.15; N, 5.10.

The sodium salt of the *p*-methoxyphenyl ester of 3,6-endoxo-Δ^4-tetrahydrophthalic acid was so unstable that it could not be recrystallized or converted to its free acid. Data establishing the nature of this ester are given in the results section.

Kinetics Methods. (A).—The rates of solvolysis of the mono-*p*-bromophenyl esters as well as the mono-*p*-methoxyphenyl succinate esters were followed by mixing the reactants in quartz cuvettes placed in a thermostated spectrophotometer and observing the optical density change at the appropriate wave length.[53]

(B).—The solvolysis of the mono-*p*-methoxyphenyl esters of maleic acid and *exo*-3,6-endoxo-Δ^4-tetrahydrophthalic acid were followed by a procedure previously described for the solvolysis of *n*-propyl-γ-(4-imidazolyl)-thiol butyrate.[15]

(C).—The titrimetric procedure employed for determination of the solvolysis constants of the anhydrides has been described previously.[14-16]

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(53) T. C. Bruice and M. F. Mayahi, THIS JOURNAL, **82**, 3067 (1960).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY, EVANSTON, ILL.]

The Mechanism of the Thermal Decomposition Reaction of Azines

BY HOWARD E. ZIMMERMAN[1] AND S. SOMASEKHARA

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The thermal decomposition of benzalazines with loss of nitrogen to afford stilbenes has been shown to proceed by an ionic chain mechanism, in which an aryldiazomethane molecule is the chain transfer species. The decomposition of unsymmetrical azines as well as of a mixture of two symmetrical azines leads to non-statistical mixtures of all three possible stilbenes under reaction conditions where neither the reactant azines nor the product stilbenes equilibrate. The minimum reaction temperature is dramatically lowered by 150° on introduction of a phenyldiazomethane catalyst.

The first report of the pyrolytic reaction of benzalazines to afford stilbenes was in 1889 by Curtius and Jay,[2] who described the conversion of benzalazine itself to stilbene.

$$C_6H_5CH{=}\ddot{N}{-}\ddot{N}{=}CHC_6H_5 \longrightarrow C_6H_5CH{=}CHC_6H_5 + :N{\equiv}N:$$

Subsequently, further examples were provided by Meisenheimer,[3] Pascal[4] and most recently by Howard and Hilbert.[5] Surprisingly little interest was exhibited in the mechanism of the reaction, perhaps because of its superficial simplicity.

Nevertheless, the literature afforded several pieces of mechanistically pertinent information. Firstly, there was the kinetic study of Williams and Lawrence[6] in which the reaction was described as first order. Secondly, Pascal[4] had reported the pyrolysis of 4-methylbenzalazine to afford only 4-methylstilbene and no stilbene or 4,4′-dimethylstilbene, a result suggestive of an intramolecular process. Finally, of interest were du Pont patents[7] which noted that benzalazines could be used as initiators for polymerizing ethylene as well as for alkylating toluene with ethylene at high temperature; this suggested the formation of unstable organic fragments from benzalazines and seemed inconsistent with the conclusion of intramolecularity.

It was with this as background and with the goal of elucidating the reaction mechanism of the benzalazine pyrolysis reaction that the present investigation began.

Preliminary to designing of experiments to determine the reaction mechanism, the gross features of the reaction, as reported by the earlier investigators, were checked. It was confirmed that the evolution of nitrogen from benzalazine, anisalazine and from 4,4′-dimethylbenzalazine proceeded at an appreciable rate only above 295°. Also, the products were found to correspond to those reported by the earlier workers. Thus (*cf.* Table I), from benzalazine stilbene was isolated as the major product together with benzonitrile and a small quantity of 2,4,5-triphenylimidazole. Similarly, from anisalazine and from 4,4′-dimethylbenzalazine the corresponding stilbenes and nitriles were obtained.

(1) Chemistry Department, University of Wisconsin, Madison 6, Wis.

(2) T. Curtius and R. Jay, *J. prakt. Chem.*, [2] **39**, 45 (1889).

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(4) P. Pascal and L. Normand, *Bull. soc. chim. France*, [4] **9**, 1029, 1059 (19)); **11**, 21 (1912).

(5) L. B. Howard and G. E. Hilbert, THIS JOURNAL, **54**, 3628 (1932).

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