

The *gem* Effect. I. The Influence of 3-Substituents on the Rates of Solvolysis of Glutaric Anhydride. A Conformational Analysis

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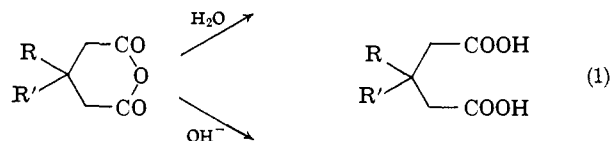
The rates of alkaline hydrolysis of a series of 15 glutaric anhydrides possessing 3-mono- and 3,3-*gem* substituents have been determined. A conformational analysis of the rate data for the alkyl-substituted anhydrides leads to the conclusion that there is little or no steric preference between the axial and equatorial positions. These results have led to the suggestion of a half-chair conformation for glutaric anhydrides. The spontaneous solvolysis constants for the monosubstituted glutaric anhydrides were also determined and found to be comparable in magnitude to the rate constants for alkaline hydrolysis.

Introduction

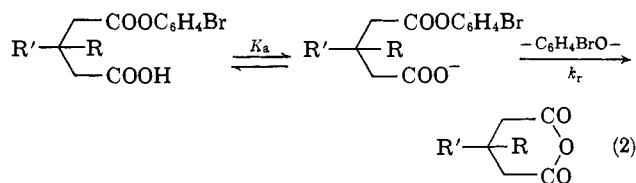
It is generally recognized that alkyl substitution promotes the formation or stability of ring compounds and that the stabilizing influence is particularly great when geminal substitution is involved ("gem effect"). On the basis of studies carried out between 1915 and 1930³ Thorpe, Ingold, and co-workers propounded the so-called Thorpe-Ingold theory of valency deviation to explain this phenomenon. The theory of valency deviation held that large substituent groups facilitated ring-closure reactions or stabilized ring compounds owing to a bond angle deformation brought about by nonbonded repulsion of the substituent groups. To date general confirmation of this theory is lacking^{4a} and a portion of the experimental data upon which it was based has been refuted.^{4b,c} Recent studies of the "gem effect" have involved studies on the formation and/or solvolysis of cyclic amines,⁵ cyclic sultones,³ cyclic ketals,⁶ and cyclic anhydrides⁷ and lactones⁸ as well as on the intramolecular hydrogen bonding of diols.⁹ Aside from possible bond angle deformation in some special cases, the most important influences of the substitution of alkyl groups on ring closure and

ring opening reside in: (a) for ring opening—steric hindrance to approach of a reactant to the seat of reaction, development of strain accompanying the opening of the ring, and change of conformation of the ring; and (b) for ring closure—decrease in nonprofitable rotamer distribution, release of strain.

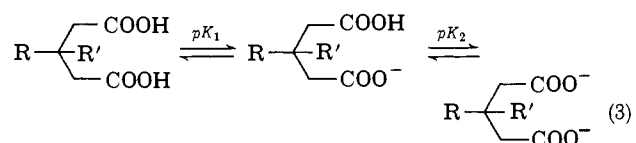
An ideal system for the quantitative evaluation of the *gem* effect would be one in which the influence of alkyl substitution could be determined on both the rates of ring formation and ring opening and in addition a thermodynamic measurement could be made to determine the closeness of the ends of the open system in the ground state. Previous experience in this laboratory^{7a} has shown that such a system is found in the rates of cyclic anhydride formation from dicarboxylic acid monoester, the rates of anhydride hydrolysis, and the pK_1 and pK_2 values of the parent dicarboxylic acids. In this and the following two parts we report our results on the spontaneous and alkaline hydrolysis of 3- and 3,3-disubstituted glutaric anhy-



drides (part I), the rates of anhydride formation from 3- and 3,3-disubstituted mono *p*-bromophenyl glutarates (part II), and the dependence of the pK_1 and



pK_2 values on the nature of 3- and 3,3-disubstitution in



glutaric acid (part III). The glutarate system is particularly suited for the quantitative determination of substituent effects.^{7a,10} Symmetrical substitution at the 3-position simplifies the stereochemistry, eliminates resonance effects, and reduces inductive effects.

Experimental Section

Compounds. Glutaric and 3,3-dimethylglutaric acids were procured from Eastman Organic Chemicals.

(10) E. Gaetjens and H. Morawetz, *ibid.*, 82, 5328 (1960).

(1) Career Investigator of the National Institutes of Health. Address correspondence to the University of California at Santa Barbara

(2) This work constitutes a portion of the Ph.D. Thesis of W. C. B.

(3) For a summary of pertinent references see F. G. Bordwell, C. E. Osborne, and R. D. Chapman, *J. Am. Chem. Soc.*, 81, 2698 (1959).

(4) (a) Some evidence for minor influences of bond angle deformations is provided from studies of 2-oxaspirane systems by S. Searles, *ibid.*, 82, 2932 (1960), and intramolecular hydrogen bonding in diols by P. von Schleyer, (see ref. 9a). (b) K. B. Wiberg and H. W. Holmquist, *J. Org. Chem.*, 24, 578 (1959). (c) H. O. Larson and G. S. K. Sung, *Australian J. Chem.*, 15, 261 (1962).

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

(6) M. S. Newman and R. J. Harper, *J. Am. Chem. Soc.*, 80, 6350 (1958).

(7) (a) T. C. Bruice and U. K. Pandit, *ibid.*, 82, 5858 (1960); (b) O. H. Wheeler and M. Almeida, *J. Org. Chem.*, 27, 4448 (1962); (c) L. Ebersson, *Acta Chem. Scand.*, 18, 534 (1964).

(8) (a) O. H. Wheeler and E. De Rodriguez, *J. Org. Chem.*, 29, 1227 (1964); (b) T. J. Daugherty, J. J. Kane, and H. Shechter, Abstracts, Division of Organic Chemistry, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan. 1964, p. 29.

(9) (a) P. von R. Schleyer, *J. Am. Chem. Soc.*, 83, 1368 (1961). (b) L. P. Kuhn, P. von R. Schleyer, W. F. Baitinger, and L. Ebersson, *ibid.*, 86, 650 (1964).

3-*n*-Propylglutaric acid and 3-isopropylglutaric acid were acquired from Frinton Laboratories. 3-Methylglutaric and 3-phenylglutaric acids were from a previous study.^{7a} 3,3-Diphenylglutaric acid was synthesized by the method of Bruce and Bradbury.¹¹ All other glutaric acids were synthesized by procedures outlined by Cope and co-workers¹² and McElvain and Clemens.¹³ See Table I for summary of physical data.

Table I. 3,3-Disubstituted Glutaric Acids (3-R,3-R'—C(CH₂COOH)₂)

R	R'	M.p., °C. (exptl.)	M.p. °C. (lit.)
CH ₃	C ₆ H ₅	140–141	140–142, ^a 142–143 ^b
C ₂ H ₅	C ₆ H ₅	112–114	114–115 ^b
<i>n</i> -C ₃ H ₇	C ₆ H ₅	130	128–131 ^b
C ₂ H ₅	C ₂ H ₅	109–110	108 ^a
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	118–119	114.5–115 ^c
<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	159–161	...
CH ₃	<i>t</i> -C ₄ H ₉	165–166°	...
CH ₃	<i>i</i> -C ₃ H ₇	99–100	...

^a S. M. McElvain and D. H. Clemens, *Org. Syn.*, **2**, 664 (1963).

^b S. M. McElvain and D. H. Clemens, *J. Am. Chem. Soc.*, **80**, 3915 (1958).

^c L. Baines and J. Thorpe, *J. Chem. Soc.*, **123**, 1209 (1923).

Ethyl 2-Cyano-3,3-diisopropylacrylate (I). A mixture of 50 g. (0.44 mole) of diisopropyl ketone, 73 g. (0.645 mole) of cyanoacetic ester, 9.2 g. (0.12 mole) of ammonium acetate, 30.6 g. (0.51 mole) of glacial acetic acid, and 150 ml. of benzene was refluxed until 11 ml. of water was collected. The mixture was then diluted with 50 ml. of benzene and washed with three 100-ml. portions of water. The combined water extracts were washed with 100 ml. of benzene; the combined benzene solutions were dried over anhydrous magnesium sulfate and, after filtering, the benzene was removed with the aid of a flash evaporator. The liquid ester was collected between 95 and 100° (2 mm.); yield 9.3 g. (10%), *n*_D²⁵ 1.4654. *Anal.* Calcd. for C₁₂H₁₉NO₂: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.79; H, 9.09; N, 6.97.

3,3-Diisopropyl-2,4-dicyanoglutarimide (II). I (11.49 g., 0.054 mole) was added to a mixture of 1.66 g. (0.072 mole) of sodium treated with 25 ml. of absolute ethanol and 5.04 g. (0.06 mole) of cyanoacetamide at room temperature. The mixture was stirred for 11 hr., allowed to stand overnight, stirred for an additional 3 hr., and diluted with 300 ml. of water. The oil was separated and the aqueous phase was extracted three times with ether. The organic phase and extracts were combined and dried over anhydrous sodium sulfate. From the ether extracts starting materials were isolated. To the aqueous solution was added 14 ml. of 6 N HCl whereupon a solid crystallized. After crystallization was judged complete, 5.6 g. (42%) was isolated; recrystallized from ethanol-water, m.p. 223–225°. *Anal.* Calcd. for C₁₃H₁₇N₃O₂: C, 63.13; H, 6.93. Found: C, 62.93; H, 7.20.

3,3-Diisopropylglutaric Acid (III). To 2 g. (8.1 mmoles) of II was added 10 ml. of concentrated sulfuric acid and 10 ml. of glacial acetic acid and the mixture

was heated to 150° when there was added carefully 2 ml. of water. After refluxing for 98 hr. the mixture was cooled, diluted with 100 ml. of water, and filtered. The filtrate was saturated with ammonium sulfate and filtered. After rinsing the filter cake with water, it was dissolved in 10% aqueous sodium carbonate and extracted with three portions of ether. The carbonate solution was decolorized with Norit on a steam bath for 15 min. and filtered. After acidifying with concentrated HCl, the solution was cooled and the product (0.77 g. (44%) of III) was collected by filtration; after recrystallization from water, m.p. 159–161°. *Anal.* Calcd. for C₁₁H₂₀O₄: C, 61.09; H, 9.32. Found: C, 60.54; H, 9.40.

*Ethyl 2-Cyano-3-methyl-3-*t*-butylacrylate (IV).* Methyl *t*-butyl ketone (50 g., 0.5 mole), 83 g. (0.74 mole) of cyanoacetic ester, 10.6 g. (0.14 mole) of ammonium acetate, 35 g. (0.58 mole) of glacial acetic acid, and 150 ml. of benzene were refluxed for 8 hr. at the end of which time 13 ml. of water was collected. The crude alkylidene ester was prepared for distillation as previously described. During the distillation 4.4 g. (5%) of the ester was collected, b.p. 70–80° (0.5 mm.), *n*_D²⁴ 1.4677. *Anal.* Calcd. for C₁₁H₁₇NO₂: C, 67.31; H, 8.73; N, 7.14. Found: C, 67.24; H, 8.69; N, 7.36.

*3-Methyl-3-*t*-butyl-2,4-dicyanoglutarimide (V).* IV (3.69 g., 0.019 mole) was allowed to react with 3.2 g. (0.038 mole) of cyanoacetamide and 0.97 g. (0.042 mole) of sodium in 50 ml. of absolute ethanol for 12 hr. The mixture was poured into 200 ml. of water and 10 ml. of concentrated HCl was added. The pink precipitate was collected by filtration, sucked dry, slurried with 25% aqueous ethanol, rinsed with water, recollected by filtration, and dried in a vacuum oven; yield 3.5 g. (80%); recrystallized from ethyl acetate-benzene as a white powder, m.p. 264–265° dec.; recrystallized from ethanol-water as white flakes, m.p. 264–265°. *Anal.* Calcd. for C₁₂H₁₅N₃O₂: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.77; H, 6.56; N, 18.24.

*3-Methyl-3-*t*-butylglutaric Acid (VI).* V (3 g., 0.0129 mole) was added to 50 ml. of a 70% aqueous sulfuric acid solution (w./v.) and the mixture was refluxed for 8 hr. and allowed to stand overnight. The reaction mixture was diluted with 25 ml. of water, saturated with ammonium sulfate, and extracted three times with ether. The combined ether extracts were dried over powdered anhydrous sodium sulfate, the ether was removed, and the product was recrystallized from water (Norit treatment). In this manner VI was obtained as white prisms, yield 1.8 g. (69%), m.p. 165–166°. *Anal.* Calcd. for C₁₀H₁₈O₄: C, 59.38; H, 8.97. Found: C, 59.09; H, 8.79.

Ethyl 2-Cyano-3-methyl-3-isopropylacrylate (VII). Methyl isopropyl ketone (50 g., 0.58 mole), 96 g. (0.85 mole), cyanoacetic ester, 12.3 g. (0.16 mole), ammonium acetate, 40 g. (0.67 mole), glacial acetic acid, and 150 ml. of benzene were refluxed for 6.5 hr. during which time 15 ml. of water was collected. Crude VII was prepared for distillation as before. Fraction collected between 67 and 75° (0.6 mm.) weighed 56.6 g. (54%), *n*_D²⁴ 1.4662. *Anal.* Calcd. for C₁₀H₁₅NO₂: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.30; H, 8.36; N, 7.87.

(11) T. C. Bruce and W. C. Bradbury, *J. Org. Chem.*, **28**, 3403 (1963).

(12) A. C. Cope, *et al.*, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

(13) S. M. McElvain and D. H. Clemens, *ibid.*, **80**, 3915 (1958).

Table II. 3-R,3-R'-Glutaric Anhydrides Properties and Analyses

R'	R	Exptl. m.p. (or b.p.), °C. (mm.)	Lit. m.p., °C.	Anal., %				Other
				Calcd.		Found		
				C	H	C	H	
H	H	54-55	55-57 ^a , 52-55 ^b	Prisms
CH ₃	H	45-46	46-47 ^c	56.24	6.29	56.20	6.34	White needles
<i>n</i> -C ₃ H ₇	H	111-112 (0.65)	<i>n</i> ²⁵ D 1.4629
<i>i</i> -C ₃ H ₇	H	109 (0.55)	<i>n</i> ²³ D 1.4672
C ₆ H ₅	H	106-107	101 ^d	69.46	5.30	70.54	5.41	White needles
C ₆ H ₅	CH ₃	99-100	...	70.57	5.92	70.51	5.96	White flakes
CH ₃	CH ₃	124-125	123-124 ^e	White flakes
C ₆ H ₅	C ₂ H ₅	69-70	...	71.54	6.47	71.49	6.57	Prisms
<i>i</i> -C ₃ H ₇	CH ₃	42-43	41-42 ^f	63.51	8.29	63.10	8.25	White flakes
C ₆ H ₅	<i>n</i> -C ₃ H ₇	88-89	...	72.39	6.94	72.47	6.97	White needles
<i>i</i> -C ₄ H ₉	CH ₃	80-81	...	65.19	8.76	65.39	8.82	White flakes
<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	Room temp.	...	66.64	9.15	66.63	9.10	Semocrystalline
C ₂ H ₅	C ₂ H ₅	98-99 (0.2)	...	63.51	8.29	63.63	8.37	<i>n</i> ²⁴ D 1.4673
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	120 (0.6)	24-25 ^g	66.64	9.15	66.85	9.20	<i>n</i> ²⁴ D 1.4654
C ₆ H ₅	C ₆ H ₅	147-148 ^h	...	76.64	5.30	76.88	5.32	White flakes

^a E. E. van Tamelen and E. E. Smisomon, *J. Am. Chem. Soc.*, **75**, 2031 (1953). ^b H. D. Zook and J. A. Knight, *ibid.*, **76**, 2302 (1954). ^c J. Cason, *et al.*, *J. Org. Chem.*, **14**, 147 (1949). ^d M. L. Woltram, *Proc. Natl. Acad. Sci. U. S.*, **40**, 794 (1954). ^e R. F. Brown and N. van Gulick, *J. Am. Chem. Soc.*, **77**, 1079 (1955). ^f R. Kon and J. Thorpe, *J. Chem. Soc.*, **117**, 1465 (1919). ^g L. Baines and J. Thorpe, *ibid.*, **123**, 1209 (1923).

3-Methyl-3-isopropyl-2,4-dicyanoglutarimide (VIII). VII (44.2 g., 0.244 mole) was added to 41 g. (0.488 mole) of cyanoacetamide and 11.13 g. (0.488 mole) of sodium in 225 ml. of absolute ethanol. After stirring for 2 days, the reaction mixture was poured into 900 ml. of water and 50 ml. of concentrated HCl was added. After isolating solids and drying at 60° in an oven, the crude yield was 65.6 g.; recrystallized from ethanol-water as fine prisms, m.p. 239-240°. *Anal.* Calcd. for C₁₁H₁₃N₃O₂: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.20; H, 6.08; N, 19.24.

3-Methyl-3-isopropylglutaric Acid (IX). To 50 g. (0.228 mole) of VIII was added 75 g. of concentrated sulfuric acid. After the sulfuric acid began to react at room temperature, 15 ml. of water was carefully added; there was a vigorous reaction with gas evolution. After adding 20 ml. of 70% aqueous sulfuric acid (w/v.), the mixture was refluxed for 9 hr. There resulted a black, gummy mass suspended in the aqueous medium. The reaction mixture was cooled, saturated with ammonium sulfate, and extracted with ether which was gravity filtered. The ether solution was decolorized with Norit at room temperature, filtered, and dried over sodium sulfate. The ether was removed and the crystalline residue was taken up with 10% aqueous sodium carbonate. Solids were removed by filtration and the filtrate was acidified with 55 ml. of concentrated HCl; collected 23.5 g. (55%) of IX which was recrystallized twice from water, m.p. 99-100°. *Anal.* Calcd. for C₉H₁₆O₄: C, 57.43; H, 8.57. Found: C, 57.29; H, 8.57.

Anhydrides. 3,3-Dimethylglutaric anhydride was acquired from Eastman Organic Chemicals. 3,3-Diphenylglutaric anhydride was prepared in a previous study.¹¹ All other anhydrides were prepared by the following general procedure. The appropriate glutaric acid was refluxed (bath temperature 120-160°) in an excess of freshly distilled acetic anhydride for at least 2 hr. and allowed to stand overnight when the excess acetic anhydride was removed by flash evaporation. When possible, the anhydrides were distilled; otherwise, they were recrystallized from benzene-petroleum ether (b.p. 60-70°) several times (Norit treatment where

necessary) and stored in a desiccator over anhydrous calcium chloride. Pertinent properties and analysis may be found in Table II.

3,3-Diisopropylglutaric Anhydride. The amount of liquid anhydride was too small to distil and the boiling point at atmospheric pressure was too high to purify by vapor phase chromatography. Low-temperature recrystallization was the purification technique employed. The apparatus used was a jacketed tube (open at top) fitted with a fritted disk and stopcock at the bottom. An ether solution of anhydride was added to the inner tube and cooled by a Dry Ice-acetone bath in the outer jacket until desired crystallization was obtained. During the recrystallization period nitrogen was passed into a filtering flask, which was used as the receiver, and through the stopcock and fritted disk. Passing nitrogen through the system in this manner prevented crystallization in the fritted portion of the funnel and also kept the solution above the fritted disk. To filter off solvent, a water aspirator was attached to the filter flask. The crystals were washed with cold ether and eluted with warm ether. The ether solution was dried over anhydrous sodium sulfate and filtered, and the ether was removed. This technique gave an analytically pure sample (Table II).

Apparatus. The solvolysis reactions were followed at constant pH by titration employing a Radiometer TTT-1b autotitrator equipped with a PHA 630 Ta scale expander, SBR2c titrigrath, and a Radiometer SBU 1a micrometer syringe drive which accommodated a 0.5-ml. Agla Trubore syringe which led to a three-neck Metrohm microtitration cell by way of a glass capillary. The glass capillary buret tip, extending halfway into the solution to be titrated, was passed through an airtight fitting. The other two necks of the cell were fitted with a Metrohm-type X glass electrode and a salt bridge (0.1 N KCl) which was fitted with an asbestos wick to prevent large changes in ionic strength during the course of solvolysis. The jacketed reaction cell had a 2-ml. capacity and was maintained at constant temperature by circulation of water from a Haake water bath which permitted temperature con-

trol at $35.0 \pm 0.1^\circ$. The syringe assembly and titration cell were enclosed in a Faraday cage.

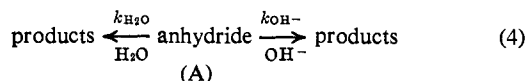
Kinetics. The base used for titration of acid accompanying anhydride solvolysis was prepared in the following manner. Carbonate-free 0.1 N KOH (4 ml.)¹⁴ was diluted to 10 ml. with decarbonated, ion-free distilled water and diluted again with 10 ml. of purified dioxane.¹⁵ The final base concentration was about 0.02 N KOH. The anhydride solutions were made by adding with the end of a small spatula about 1 mg. of anhydride to the titration cell and carefully dissolving the sample in about a 2-ml. aliquot of a 0.1 N KCl [50% aqueous dioxane (v./v.)] solution. The KCl solution was made by diluting 10 ml. of 0.2 N aqueous KCl with 10-ml. of pure dioxane. Volumetrics (10 ml.) were used for all dilutions. 3,3-Diphenylglutaric anhydride was only partially soluble in 50% dioxane-water; therefore, 75% dioxane-water (v./v.) was used, 5 ml. of aqueous 0.4 N KCl was diluted to 20 ml. with pure dioxane. The base was diluted so as to be about 0.02 N KOH in 75% dioxane-water. Dioxane-deuterated water solutions (50%) were prepared in the same manner as 50% dioxane-water. Before the titration, the mixture was stirred to ensure complete solution of the anhydride and nitrogen was passed through the cell for approximately 5 min. to give a carbon dioxide free atmosphere. The solution was then brought to the titrating pH and the amount of base added per unit of time, to maintain constant pH, recorded.

The system was standardized periodically at pH 6.96 with Fisher Scientific pH 7 buffer. Since only the relative values of the rate constants were important this was the only buffer used.

First-order rate constants were generally determined by the method of Guggenheim.¹⁶ A few constants were calculated by the integrated form of the first-order rate equation when an accurate knowledge of the amount of base added as t_∞ was known. For the studies in D₂O at 35° the pD values were taken as the pH meter readings plus the proper electrode correction.¹⁷

Results

The kinetics for the solvolysis of glutaric anhydrides at alkaline pH can be represented by eq. 4-6, where



$$-\frac{d(A)}{dt} = k_{\text{H}_2\text{O}}(A) + k_{\text{OH}^-}(A)(\text{OH}^-) \quad (5)$$

$$-\frac{d(A)}{dt} = k_{\text{H}_2\text{O}}(A) + k_{\text{OH}^-}(A) \frac{K_{\text{WD}}}{a_{\text{H}}} \quad (6)$$

$k_{\text{H}_2\text{O}}$ is the rate constant for spontaneous water solvolysis, k_{OH^-} is the rate constant for hydroxide ion catalyzed hydrolysis, a_{H} is the hydrogen ion activity as

(14) The carbonate-free base was prepared as outlined: A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 52.

(15) Purified dioxane was prepared by the method of Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1957, p. 285.

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

(17) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

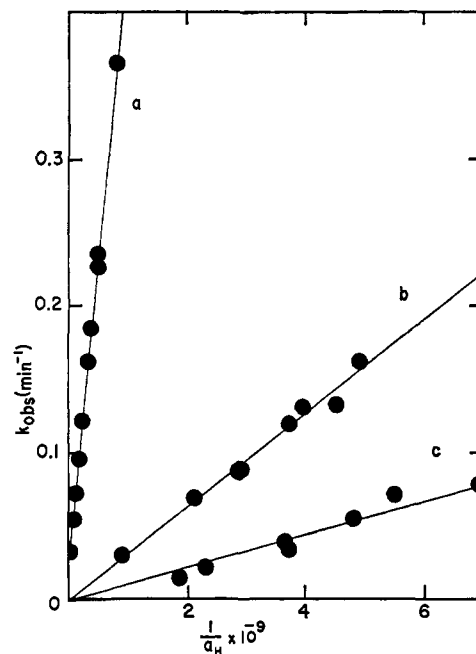


Figure 1. Examples of plots of k_{obsd} vs. $1/a_{\text{H}}$, from which the slopes give the rate constants for alkaline-catalyzed hydrolysis ($K_{\text{WD}}k_{\text{OH}^-}$) and the intercepts (only for the monosubstituted glutaric anhydrides) give the rate constants for spontaneous solvolysis ($k_{\text{H}_2\text{O}}$): a, glutaric anhydride; b, 3,3-dimethylglutaric anhydride; c, 3,3-diisopropylglutaric anhydride.

measured by the glass electrode, and K_{WD} is the autoprotolysis constant of water in 50% aqueous dioxane. The pseudo-first-order rate constants (k_{obsd} , see Table III) when plotted against $1/a_{\text{H}}$ provided linear plots as shown in Figure 1. From the slopes of plots in Figure 1 were calculated the values of $K_{\text{WD}}k_{\text{OH}^-}$ and from the intercepts the values of $k_{\text{H}_2\text{O}}$. All slope and intercept values used in this study were determined by the method of least squares.¹⁸ A knowledge of the true value of K_{WD} is not necessary since for our correlative purposes relative rates suffice. For unsubstituted and 3-monosubstituted glutaric anhydrides there is a significant water rate competing with the hydroxyl rate. For instance, for glutaric anhydride at pH 9, 5-10% of the observed pseudo-first-order rate constant pertains to spontaneous solvolysis. The spontaneous rate was not determined for the 3,3-disubstituted glutaric anhydrides. The rate data relative to glutaric anhydride are listed in Table III; a comparison is also made with pertinent literature studies.

Discussion

In the pH range investigated and in 50% dioxane-water (v./v.) glutaric anhydrides undergo hydrolysis *via* hydroxide ion catalysis and spontaneous water solvolysis (eq. 4). The spontaneous water solvolysis is associated with a deuterium solvent isotope effect ($k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$) of 2.9 which suggests a mechanism involving proton abstraction in the transition state (*i.e.*, water acting as a general base catalyst to assist the nucleophilic displacement by a water molecule).^{7c} The deuterium solvent isotope effect for alkaline hydrolysis was calculated from eq. 7, where k_2^{H} and

(18) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

Table III. Rates of Solvolysis of 3,3R,R'-Disubstituted Glutaric Anhydrides ($\mu = 0.1 M$ with KCl, $T = 30^\circ$)

R	R'	pH range employed	Solvent (v./v.)	No. of k_{obsd} determinations	Relative rate constants ^a		Correlation coefficient	Lit.
					k'_{OH}	$k'_{\text{H}_2\text{O}}$		
H	H	6.56-8.90	50% dioxane-H ₂ O	37	1.00 ± 0.019	1.00 ± 0.03	1.00	1.00
		8.26-8.85	75% dioxane-H ₂ O	5	1.00 ± 0.097	1.00 ± 0.11	0.98	{0.63, ^b (0.70), ^c (0.61) ^d }
H	CH ₃	8.18-8.74	50% dioxane-H ₂ O	7	0.625 ± 0.036	0.51 ± 0.07	0.99	
H	<i>n</i> -C ₃ H ₇	8.26-8.65	50% dioxane-H ₂ O	4	0.598 ± 0.020	0.21 ± 0.04	1.00	
H	C ₆ H ₅	6.96-7.99	50% dioxane-H ₂ O	3	1.096 ± 0.096	1.48 ± 0.05	0.99	{0.077, ^b (0.11), ^c (0.074) ^d }
H	<i>i</i> -C ₃ H ₇	7.88-8.68	50% dioxane-H ₂ O	11	0.536 ± 0.024	0.48 ± 0.03	0.99	
CH ₃	CH ₃	8.94-9.70	50% dioxane-H ₂ O	9	0.0757 ± 0.0041	...	0.99	
CH ₃	<i>i</i> -C ₃ H ₇	9.30-9.74	50% dioxane-H ₂ O	6	0.0574 ± 0.0034	...	0.99	0.057, ^b (0.045) ^c
CH ₃	<i>t</i> -C ₄ H ₉	9.24-9.69	50% dioxane-H ₂ O	8	0.0502 ± 0.0027	...	0.99	
CH ₃	C ₆ H ₅	9.19-9.75	50% dioxane-H ₂ O	8	0.0911 ± 0.0047	...	0.99	
C ₂ H ₅	C ₆ H ₅	9.31-9.73	50% dioxane-H ₂ O	7	0.0752 ± 0.0065	...	0.98	
<i>n</i> -C ₃ H ₇	C ₆ H ₅	9.30-9.74	50% dioxane-H ₂ O	7	0.0673 ± 0.0060	...	0.98	
<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	9.27-9.86	50% dioxane-H ₂ O	8	0.0302 ± 0.0025	...	0.98	
C ₂ H ₅	C ₂ H ₅	8.99-9.98	50% dioxane-H ₂ O	6	0.0548 ± 0.0040	...	0.99	
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	9.58-9.95	50% dioxane-H ₂ O	3	0.0508 ± 0.0003	...	1.00	
C ₆ H ₅	C ₆ H ₅	9.67-9.96	75% dioxane-H ₂ O	5	0.0603 ± 0.0034	...	0.99	

^a $k'_{\text{OH}} = (k_{\text{OH}}K_{\text{WD}})/(k'_{\text{OH}}K_{\text{WD}}^0)$; $k_{\text{H}_2\text{O}} = (k_{\text{H}_2\text{O}})/(k'_{\text{H}_2\text{O}})$ where rates for glutaric anhydride are indicated by the superscript 0. $k'_{\text{OH}}K_{\text{WD}}^0 = 4.16 \pm 0.08 \times 10^{-10} \text{ l. mole}^{-1} \text{ min.}^{-1}$; $k_{\text{H}_2\text{O}} = 3.51 \pm 0.11 \times 10^{-2} \text{ min.}^{-1}$ (50% dioxane-water), and $k'_{\text{OH}}K_{\text{WD}}^0 = 0.699 \pm 0.068 \times 10^{-10} \text{ l. mole}^{-1} \text{ min.}^{-1}$; $k_{\text{H}_2\text{O}} = 1.22 \pm 0.14$ (in 75% dioxane-water). ^b See ref. 7c, $k'_{\text{H}_2\text{O}}$ at 30°, pH-Stat method. ^c See ref. 7b, $k_{\text{H}_2\text{O}}$ at 56.7°, conductometric method. See ref. 7c for inadequacies of this method. ^d See ref. 7a, 28% ethanol-water at 35°.

$$\frac{k_{\text{OH}}}{k_{\text{OD}}} = \frac{k_2^{\text{H}} K_{\text{D}_2\text{O}}}{k_2^{\text{D}} K_{\text{H}_2\text{O}}} \quad (7)$$

k_2^{D} are the slopes of plots of k_{obsd} vs. $1/a_{\text{H}}$ and $1/a_{\text{D}}$, respectively, and the ratio of $K_{\text{D}_2\text{O}}/K_{\text{H}_2\text{O}}$ is assumed to be that for the ratio of autoprotolysis constants of pure D₂O and pure H₂O.¹⁹ The value of $k_{\text{OH}}/k_{\text{OD}}$ was determined to be 0.60, in agreement with expectations for a BAC2 mechanism.²⁰

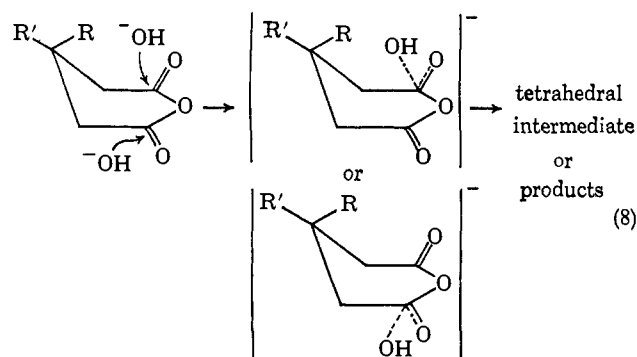
Attempts to determine the value of the rate constant for spontaneous hydrolysis for all the substituted glutaric anhydrides of this study were not made. For this reason consideration of structure-reactivity relationships pertain to the data for alkaline hydrolysis. It has been proposed previously that the mechanism for the alkaline hydrolysis of carboxylic acid anhydrides involves rate-determining nucleophilic addition of hydroxide ion to the acyl carbonyl group through a 90° transition state of mainly sp² character followed by rapid ring opening to yield hydrolysis products.²¹

The suggestion of the sp² character of the transition state by Bruce and Pandit^{2a} was tested by Hall^{21a} who showed that an anhydride possessing demonstrable ring strain hydrolyzed at a rate comparable to that of a structurally related anhydride that did not possess ring strain. The data of the present study is best interpreted on the basis of a transition state possessing appreciable sp³ hybridization. Inspection of eq. 8 reveals that hindrance of OH⁻ attack should only occur when the attack is from above if the transition state is sp² in character. From Table III it is apparent that k'_{OH} decreases to as small a factor as 0.03. If the transition state possesses appreciable sp³ character, then its formation from top or bottom side attack would be accompanied by 1,3-interaction of the attacking OH⁻ or the carbonyl oxygen with R and relative rates appreciable smaller than 0.5 would be anticipated.

(19) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p. 188.

(20) (a) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960); (b) T. C. Bruce and T. H. Fife, *J. Am. Chem. Soc.*, **84**, 1973 (1962).

(21) (a) H. K. Hall, Jr., *J. Org. Chem.*, **28**, 2027 (1963); (b) see also ref. 7.



To evaluate the importance of steric and polar effects of R and R' in eq. 8 the linear free-energy equation of Taft²² was employed (eq. 9). In eq. 9 ρ^* and δ are

$$\log \frac{k}{k_0} = \rho^* \sigma^* + \delta E_s \quad (9)$$

reaction constants and quantitatively indicate the relative susceptibility of a reaction mechanism to polar and steric effects of substituents. The ρ^* and E_s values are polar and steric substituent constants, respectively, evaluated by Taft from the well-investigated hydrolysis of esters of type RCOOR'. The σ^* values employed to evaluate the importance of polar effects in anhydride hydrolysis were for RCH₂CH₂ and the E_s values employed were for R. For 3,3-disubstituted glutaric anhydrides the ρ^*_{LS} (L = large group, S = small group) values were taken to be equal to σ^* of R plus σ^* of R'. In Table IV there is recorded the values of σ^*_{LS} , E_s for the smaller substituent (E_s^{S}) and E_s for the larger substituent (E_s^{L}) used in this study.

Inspection of the σ^*_{LS} values of Table IV reveals that their range is small and that for the alkyl substituents the range of σ^*_{LS} values falls within the median deviation of values (± 0.02 to ± 0.04) that Taft assigns to his tabulation of original σ^* values. In addition, the

(22) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 587.

Table IV. Polar and Steric Substituent Constants for 3-R,3-R'-Glutaric Anhydride

R	R'	σ^*_{LS}	E_s^S	E_s^L
H	H	0.000	0.00	0.00
H	CH ₃	-0.015	0.00	-1.24
H	C ₂ H ₅	-0.030	0.00	-1.31
H	<i>n</i> -C ₃ H ₇	...	0.00	-1.60
H	<i>i</i> -C ₃ H ₇	...	0.00	-1.71
H	C ₆ H ₅	+0.180	0.00	...
CH ₃	CH ₃	-0.030	-1.24	-1.24
CH ₃	<i>i</i> -C ₃ H ₇	...	-1.24	-1.71
CH ₃	<i>t</i> -C ₄ H ₉	...	-1.24	-2.78
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	...	-1.60	-1.60
C ₂ H ₅	C ₂ H ₅	-0.060	-1.31	-1.31
<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	...	-1.71	-1.71
CH ₃	C ₆ H ₅	+0.165	-1.24	...
C ₂ H ₅	C ₆ H ₅	+0.150	-1.31	...
<i>n</i> -C ₃ H ₇	C ₆ H ₅	...	-1.60	...
C ₆ H ₅	C ₆ H ₅	+0.360

value of ρ^* may be approximated to be 0.2. Therefore, a consideration of polar effects (at least insofar as alkyl substituents are concerned) may be dispensed with, reducing eq. 9 to eq. 10. In the case of the phenyl

$$\log \frac{k}{k_0} = \delta E_s \quad (10)$$

group which has the largest σ^* (+0.18) a polar effect must be considered. The reduction in p*K* for 3-phenylpropionic acid when compared to propionic acid or 3-alkylpropionic acids verifies the existence of a significant polar effect (Table V). In glutaric anhydride

Table V. ΔpK Data for Some 3-Substituted Propionic Acids (RCH₂CH₂COOH)^a

R	p <i>K</i> ^b	ΔpK
C ₆ H ₅	4.66	0.00
H	4.88	0.22
CH ₃	4.82	0.16
C ₂ H ₅	4.86	0.20
<i>n</i> -C ₃ H ₇	4.88	0.22
		Av. 0.20

^a H. C. Brown, *et al.*, in "Determination of Organic Structures by Physical Methods," Braude and Nachod, Ed., Academic Press, Inc., New York, N. Y., 1955. ^b Thermodynamic values.

the substitution of alkyl or H in a 3-position by the larger phenyl group appears to enhance the rate of solvolysis (compare R = R' = H to R = H, R' = C₆H₅; R = R' = CH₃ to R = CH₃, R' = C₆H₅; etc.). Clearly, the steric effect of the phenyl group is compensated for by some polar effect which may take place by induction or by a direct interaction of the phenyl group with the anhydride group.

If glutaric anhydride exists in a chair conformation, as proposed,²³ the substituent groups R and R' may assume axial and equatorial conformations. The steric effect of R and R' will depend, therefore, not only on their bulk but also on the conformational equilibrium constant *K_E* between L_eS_a and L_aS_e (e = equatorial, a = axial, L = large substituent, S = small substituent). This complicating factor is alleviated for those anhydrides for which R = R'. In Figure 2 there is plotted the log of the relative rate con-

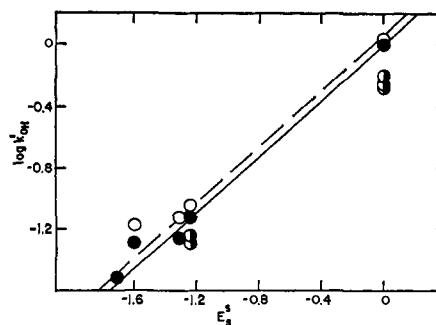


Figure 2. A plot of the Taft steric substituent constant (E_s) for the smallest substituent in 3- and 3,3-disubstituted glutaric anhydrides vs. the log of the relative rates of alkaline hydrolysis: ●, R = R'; ○, R = C₆H₅ and R' = H or alkyl; ◐, other unsymmetrically substituted anhydrides).

stants for anhydride solvolysis vs. E_s^S . All the anhydride data (except R = R' = C₆H₅) is included in Figure 2. The least-square (solid) line has been drawn through the points for R = R' (dark circles, without taking into account the unsymmetrically substituted anhydrides (○, phenylalkyl or phenyl hydrogens; ◐, dialkyl). For the unsymmetrically substituted anhydrides the E_s values used were for the smallest substituent (E_s^S). The value of δ obtained as the slope of the plot of Figure 2 for symmetrically substituted anhydrides (solid line) was found to be $+0.905 \pm 0.035$ ($r = 0.999$). In evaluating δ , the E_s value of Taft for *n*-propyl was not employed for it is obviously too large for the present system (see Figure 2 and compare rates where R = R' = C₂H₅ and *n*-C₃H₇ (Table V)). The relative rate for the alkaline hydrolysis of 3,3-diphenylglutaric anhydride was also not employed in determining δ since Taft does not list an E_s value for the phenyl group. From Figure 2 a corrected E_s value for *n*-C₃H₇ (-1.41) may be extrapolated. Before an E_s value for the phenyl group can be determined from the regression line (solid line) in Figure 2 using $\log k'$ for when R = R' = C₆H₅, a correction for a significant polar effect (+0.36) must be made. Since the polar effect might be expected to remain relatively constant (see Table V) for when R = H or alkyl and R' = phenyl, the intercept value at $E_s^S = 0$ calculated from a regression line ($\delta = 0.87 \pm 0.08$, $r = 0.986$) through the points for these compounds (broken line, Figure 2) can be assumed to be equal to $\rho^*\sigma^* = +0.034$. If the polar effect doubles when R = R' = C₆H₅ then the $\rho^*\sigma^*$ term should double (+0.07). Using this value as a correction for polar effects and the $\delta = +0.90$ calculated for R = R' = alkyl eq. 9 gives an E_s for phenyl of -1.44. The value of $\delta = +0.905 \pm 0.035$ can be compared with $\delta = 0.99$ (85% aqueous ethanol) and $\delta = 0.957$ (85% aqueous DMSO) determined by Roberts in a study of the saponification of esters of the type RCOOC₂H₅.²⁴

Having obtained the δ value from the symmetrically substituted anhydrides we are now in a position to determine the conformational equilibria for the unsymmetrically substituted anhydrides by employing a kinetic scheme of the type used by Winstein and

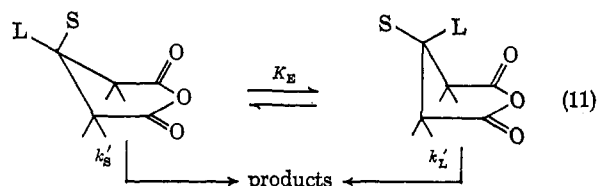
(23) J. W. LeFevre and A. Sundaram, *J. Chem. Soc.*, 4009 (1962).

(24) J. D. Roberts, *J. Org. Chem.*, 29, 2714 (1964).

Table VI. Summary of Conformational Equilibrium Constants (K_E)

L	S	K_E	$\frac{\% k'_S =}{K_E + 1}$	$\frac{\% k'_L =}{100K_E + 1}$
CH ₃	H	0.68 ± 0.10	60 ± 4	40 ± 4
<i>n</i> -C ₃ H ₇	H	0.74 ± 0.06	57 ± 1	43 ± 1
<i>i</i> -C ₃ H ₇	H	0.91 ± 0.10	52 ± 2	48 ± 2
<i>i</i> -C ₃ H ₇	CH ₃	0.63 ± 0.21	61 ± 15	39 ± 15
<i>t</i> -C ₄ H ₉	CH ₃	0.52 ± 0.09	65 ± 3	35 ± 3
C ₆ H ₅	H	(-0.096 ± 0.096)
		(1.045 ± 0.096)		
C ₆ H ₅	CH ₃	(-0.0155 ± 0.0047)
		(0.0334 ± 0.0047)		
C ₆ H ₅	C ₂ H ₅	(-0.0101 ± 0.0065)
		(0.0074 ± 0.0065)		
C ₆ H ₅	<i>n</i> -C ₃ H ₇	(-0.0085 ± 0.0060)
		(0.0069 ± 0.0060)		

Holness²⁵ for the conformational analysis of cyclohexane derivatives (eq. 11). In eq. 11, k'_S and k'_L are relative rate constants (relative to glutaric anhydride) for the alkaline hydrolysis of the indicated conformers



which are in equilibrium *via* the constant K_E . From eq. 11 the relative rate of alkaline hydrolysis (k'_{OH}) is provided by eq. 12. Since we have shown that polar

$$k'_{OH} = \frac{k'_S}{K_E + 1} + \frac{k'_L K_E}{K_E + 1} \quad (12)$$

effects may be ignored (except possibly for phenyl) and, if a chair conformation is involved, only the axial substituent can block attack of hydroxide ion or formation of the transition state. For the anhydride system eq. 9 can be written as in eq. 13. Substituting eq. 13

$$\begin{aligned} \log k'_S &= \delta E_s^S \\ \log k'_L &= \delta E_s^L \end{aligned} \quad (13)$$

into eq. 12 we obtain

$$k'_{OH} = \frac{10^{\delta E_s^S}}{K_E + 1} + \frac{K_E 10^{\delta E_s^L}}{K_E + 1} \quad (14)$$

and

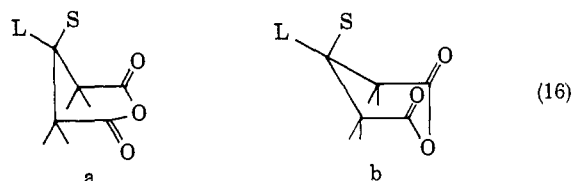
$$K_E = \frac{(10^{\delta E_s^S} - k'_{OH})}{(k'_{OH} - 10^{\delta E_s^L})} \quad (15)$$

The value of δ in eq. 14 is that previously determined for the case of $R = R'$ since for these symmetrically substituted anhydrides $K_E = 1$ and eq. 14 reduces to eq. 10. Equation 15 can, therefore, be solved for K_E (Table VI). Values of K_E for $L = \text{phenyl}$ and $S = \text{alkyl}$ or hydrogen could not be determined because the difference between small numbers using eq. 15 is approaching the magnitude of the experimental error. A small polar effect by the phenyl group could account for the negative values that would be obtained for K_E (see Table VI) since the inclusion of a polar effect

(25) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

($\rho^* \sigma^*$) would correct the numerator to more positive values.²⁶

Inspection of the K_E values for anhydrides in which $R = \text{hydrogen}$ and $R' = \text{alkyl}$ reveals that there is no real hindrance to the larger substituent being axial and that in fact the two conformational isomers are about equally favored. In cyclohexane steric repulsion of the axial substituent by the axial hydrogen in the 3-position is more important than steric repulsion of the equatorial substituents by hydrogens in the 2-position. Thus, large substituents often²⁵ but not always²⁷ assume the equatorial conformation. If one assumes that glutaric anhydride may have either a half-chair conformation (eq. 16a) or a chair conformation (eq. 16b) then for eq. 16b there should be steric repulsion between the axial substituent and the π clouds of the carbonyl carbons²⁸ while in eq. 16a there should



be less repulsion of the axial substituent. In eq. 16a the equatorial substituent is more nearly eclipsed by the hydrogens in the 2-position than in eq. 16b. Therefore, if the anhydride has the chair conformation large substituents in the 3-position should prefer the equatorial position due to 1-3 interaction as in cyclohexane. The conformational preference of the *t*-butyl substituent in cyclohexane is equatorial by a minimal value of 5.4-5.8 kcal. mole⁻¹.²⁵ That the conformational equilibrium for glutaric anhydride when $L = t\text{-C}_4\text{H}_9$ and $S = \text{CH}_3$ is so large (Table VI) suggests that the favored conformation is that of the half-chair form (eq. 16a). In eq. 16a the collinearity of the anhydride OCOO atoms would provide resonance stability and there would appear to be less preference of a large group for the axial or equatorial position since 1-3

(26) The small K_E value suggested for when $R = \text{H}$ and $R' = \text{C}_6\text{H}_5$ (Table VI) could mean that C_6H_5 remains primarily equatorial; the rationale for this is not obvious to the authors.

(27) See, for example, F. R. Jensen and L. H. Gale, *J. Am. Chem. Soc.*, **81**, 6337 (1959).

(28) For a discussion of the "alkyl effect" in cyclohexanones which throws some light on steric interactions of conformational isomers with a carbonyl group see B. Rickborn, *ibid.*, **84**, 2414 (1962).

interactions are reduced and 1-2 interactions are increased over those of eq. 16b. As a test of eq. 11 and 12 and the rationale leading to the calculation of K_E , values of the relative rate constants for hydroxide ion attack on the conformers in which the large group is axial (k'_L) and equatorial (k'_S) may be calculated from the known rate constants for the symmetrically substituted anhydrides. On the basis of eq. 11 and 12 the relative rate constant k'_S should be equal to the experimentally determined relative rate constant $(k'_{OH})_{SS}$ for the symmetrical anhydride in which L = S = small substituent and in a like manner k'_L should be equal to the relative rate constant $(k'_{OH})_{LL}$ for the case when L = S = large substituent. The experimentally determined relative rate constant $(k'_{OH})_{LS}$ for any unsymmetrically substituted anhydride should then be given by eq. 17, where the mole fraction of

$$(k'_{OH})_{LS} = N_S(k'_{OH})_{SS} + N_L(k'_{OH})_{LL} \quad (17)$$

anhydride in which the axial substituent is small is given by $N_S = 1/(1 + K_E)$ and the mole fraction of anhydride in which the axial substituent is large is given by $N_L = K_E/(1 + K_E)$. Employing the K_E values of Table VI, the values of $(k'_{OH})_{LS}$ were calculated and are presented in comparison with the experimentally determined values in Table VII. The

Table VII. Summary of Calculated and Experimental Relative Rate Constants

L	S	Exptl.	Calcd.
CH ₃	H	0.625 ± 0.036	0.630
<i>n</i> -C ₃ H ₇	H	0.598 ± 0.020	0.592
<i>i</i> -C ₃ H ₇	H	0.536 ± 0.024	0.534
<i>i</i> -C ₃ H ₇	CH ₃	0.0574 ± 0.0034	0.058

agreement between the calculated and experimental values of Table VII is exceptionally good, suggesting that the ring system of the anhydride is the same in all cases, presumably the half-chair conformation

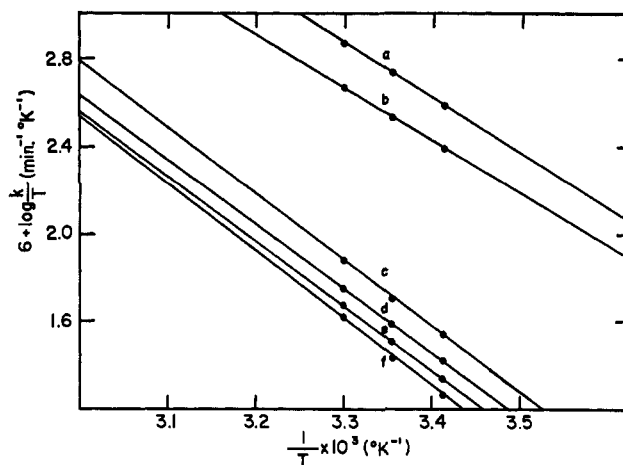


Figure 3. An activation plot of Eberson's anhydride hydrolysis data showing no isokinetic points.

suggested by this study. Furthermore, it is obvious that the group in the equatorial position does not cause any decrease in the rate of anhydride hydrolysis.

It has been suggested by Eberson^{7c} that variations in the rates of solvolysis of glutaric anhydrides at ambient temperatures may be meaningless due to the experimental temperature being too close to the isokinetic temperature (β). He suggests that when R = hydrogen and R' = alkyl, $\beta = 290^\circ\text{K}$. and when R = R' = alkyl, $\beta = 320^\circ\text{K}$. An activation plot (Figure 3) of Eberson's pertinent glutaric anhydride solvolysis data^{7c} as outlined by Petersen²⁹ to check for an isokinetic relation did not indicate such a relation since there is no single point of intersection (isokinetic temperature). Actually over the range of $1/T$ considered which includes $\beta = 290$ and 320°K , there is nothing even remotely resembling an isokinetic temperature.

Acknowledgments. This work was supported by a grant from the National Institutes of Health.

(29) R. C. Petersen, *J. Org. Chem.*, **29**, 3133 (1964).