Solvolysis of Some Substituted Glutaric Anhydrides[1]

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The rates of solvolysis of a number of alkyl substituted glutaric anhydrides have been measured conductometrically at 0, 30, and 57° in 1:5 dioxane–water. The substituted glutaric anhydrides all solvolyze at rates less than glutaric anhydride itself, and the results can be interpreted in terms of steric hindrance to solvolysis with the anhydride ring adopting a near chair conformation.

Although the solvolysis of methyl-substituted succinic anhydrides[2] (Table III) has received considerable attention, only a few data have been published on the solvolysis of glutaric anhydrides.[2c,d] This paper reports data on the rates of solvolysis of a number of α- and β-methyl and ethyl substituted glutaric anhydrides at three temperatures (see Table I) in 1:5 dioxane–water (v./v.)

The rates were determined conductometrically,[2a] rather than by the often used method of aniline titration[3] since this depends on the fact that aniline reacts completely and rapidly with the unhydrolysed anhydride, which may not be the case for substituted anhydrides. The conductometric method is dependent on the solutions of the acid formed obeying the Ostwald dilution law[4]—*i.e.*, that conductance is proportional to the concentration. The rates followed first-order rate plots, falling off slightly toward the end of the reaction. Negative catalysis by organic acids has previously been observed.[2c,5] The solvolysis was not reversible since solutions of the corresponding glutaric acids did not change in conductance and gave values the same as the final conductancies of the anhydrides at the same concentration.

TABLE I

SOLVOLYSIS OF GLUTARIC ANHYDRIDES IN PER CENT AQUEOUS DIOXANE

Anhydride	$k \times 10^5$ sec.$^{-1}$ 0°	28.2 ±·1°	56.7°	k_{rel} (at 56.7°)	E_{act}, kcal.	log PZ
Glutaric	29.7	275 (30.8°)	950	100	9.6	6.0
2-Methyl	12.1	133	433	46	8.1	4.8
3-Methyl	...	160	667	70	9.1	5.6
2,2-Dimethyl	8.11	56.3	353	38	12.2	7.4
3,3-Dimethyl	...	38.8 (25.8°)	106	11	9.0	4.8
3-Ethyl-3-methyl	...	26.7 (30.0°)	80.2	8.4	8.5	4.3
3,3-Diethyl	...	33.0	43.5	4.5	4.3	1.2

Anhydrides, including cyclic anhydrides, solvolyse by a mechanism[2c,4,6] involving the nucleophilic attack of a solvent molecule on a carbonyl carbon atom, followed by fission of the neighboring acyl–oxygen bond. The anhydrides are solvated in solution[7] and solvolysis occurs using a water molecule from the anhydride solvation shell. The kinetically discernible step will be that of the attack of the water molecule with accompanying ring opening.

The order of the rates of solvolysis found for the glutaric anhydrides in 1:5 dioxane–water at 56.7° (see Table I) was H > 3-methyl > 2-methyl > 2,2-dimethyl >> 3,3-dimethyl > 3-methyl, 3-ethyl > 3,3-diethyl, with an over-all difference of 22-fold. Comparison with previous data (see Table II) shows that the same order is followed for the few cases studied in other solvents, the decrease in rate for the 3-methyl anhydride in 28.5% ethanol being similar,[2d] although the decrease for the 3,3-dimethyl compound is greater in this solvent and in water[2c] than in ethanol.[2c]

TABLE II

SOLVOLYSIS OF GLUTARIC ANHYDRIDES IN DIFFERENT SOLVENTS

Anhydride	$k \times 10^5$ sec.$^{-1}$ 20° (H_2O ?)[a]	20° EtOH[a]	35°-pH 8.5, 28.5% EtOH—H_2O[b]	56.7°, % aqueous dioxane[c]
Glutaric	200.2	0.456	380	950
2-Methyl	...	...	...	433
3-Methyl	...	...	230	667
2,2-Dimethyl	...	...	130	353
3,3-Dimethyl	14.04	0.0470	28	106
3-Ethyl-3-methyl	...	...	...	80.2
3,3-Diethyl	...	...	...	43.5

[a] Ref. 1c. [b] Ref. 1d. [c] Present work.

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[1] Department of Chemistry, University of Puerto Rico at Mayaguez, Puerto Rico. Presented at the 8th Latinoamerican Congress of Chemistry, Buenos Aires, September, 1962.

[2] (a) A. C. D. Rivett and N. V. Sidgwick, *J. Chem. Soc.*, **97**, 1677 (1910); (b) P. E. Verkade, *Rec. trav. chem.*, **40**, 192, 199 (1921); (c) J. Koskikallio, *Ann. Sci. Fennicae, Ser. A*, **57**, 7 (1954); (d) T. C Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960).

[3] B. N. Menshutkin and A. M. Vasil'ev, *J. Russ. phys. Chem.*, **21**, 192 (1889).

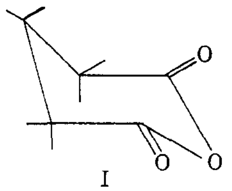
[4] V. Gold, *Trans. Faraday Soc.*, **44**, 506 (1948).

[5] M. Kilpatrick, *J. Am. Chem. Soc.*, **52**, 1410 (1930).

[6] C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960); A. R. Butler and V. Gold, *ibid.*, 2305 (1961).

[7] *Cf.* E. K. Plyler and E. S. Barr, *J. Chem. Phys.*, **3**, 679 (1935); **4**, 90 (1936); E. Tommila and S. Hietala, *Acta Chem. Scand.*, **8**, 257 (1954).

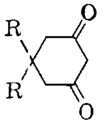
The observed decreases in rate on substitution, which are considerably greater for β-substitution, must be due to steric (or electronic) effects hindering the approach of a solvent molecule.[2d] Models indicate that the glutaric anhydride ring will adopt a deformed chair conformation (I), with


I

the part of the ring containing the oxygen bridge elevated above its position in a true chair conformation, to accommodate the increased carbonyl internal ring angle. In such a conformation one of the *gem* substituents of a 3,3-disubstituted glutaric anhydride must occupy an "axial" position, projecting above and near the carbonyl groups. Approach of a water molecule from the topside of the molecule will than be hindered and approach from the underside is impeded by the axial hydrogen on the two α-carbon atoms. 3,3-Dimethylglutaric anhydride thus undergoes solvolysis at a considerably reduced rate (ratio 1:0.11). Its steric parameter[2d] calculated from the ratio in decrease of rate, corrected for electronic effects as shown in the corresponding acid–esters, is also large. In agreement with this suggestion of steric hindrance to nucleophilic attack, the retardation is proportionally greater in ethanol (ratio 1:0.097)[2a] having larger steric requirements and in basic solution (ratio 1:0.074) (pH 8.5),[2b] where the nucleophile will be the solvated hydroxide ion. The rate decreases slightly on replacing one methyl for an ethyl group, and again further for the much more bulky 3,3-diethyl compound. In the case of the 3-ethyl-3-methyl anhydride, the ethyl substituent probably preferentially occupies the equatorial position in which it will exert little extra effect (as compared to methyl), although a certain proportion of the ethyl-axial conformation will be present. (ΔFe-a for ethyl is only slightly larger than for methyl.[8]) The decrease in rate for the 3-methyl compound is only slightly less than that anticipated from the acidity of the half acid–ester (small steric parameter[2d]) and can be attributed to the small fraction of the anhydride reacting in a methyl-axial conformation. The energies of activation and log PZ factors decrease for these compounds with increasing substitution, the log PZ factor for the 3,3-diethyl compound being exceptionally low and consistent with a greatly increased steric effect.

Part of the retardation of the α-substituted anhydrides can be attributed to the inductive (I) effect of the methyl groups, which by increasing the negative charge on the carbonyl carbon atom reduces the ease of nucleophilic attack. However 2,2-dimethylglutaric anhydride still had an appreciable steric parameter[2d] and also an increased energy of activation (see Table I). 2-Methylglutaric anhydride with one carbonyl group unhindered solvolysed at about half the rate of the unsubstituted anhydride, and its log PZ factor is lower.

The decrease in rate of alkaline ring fission of 5,5-dimethyl-1,3-cyclohexandione (II. R = Me) as compared with the unsubstituted dione (II. R = H)[9] (rates 5.4 and 133 × 10^{-5} min.$^{-1}$, respectively) must also be due to steric hindrance to nucleophilic attack on the carbonyl group.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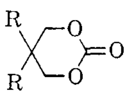
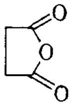
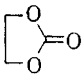

III

Alkyl substitution in the 3-position of cyclic α,γ-carbonates (III), however, results in an enhanced rate of hydrolysis with potassium carbonate,[10] (III. R = H and III, R = Me, rates 114 and 364 l. mole^{-1} min.$^{-1}$, respectively) and this has been attributed to an acceleration of hydrolysis in the unsubstituted carbonate resulting from dipole–dipole interactions in the carbonate linkage. Such interactions are reduced by the steric hindrance of 3-axial substituents and these carbonates show less tendency to polymerize.[11] Significantly 2-substitution, which bears a similar relation to the carbonyl group as does 3-substitution in the anhydrides, results in retardation of hydrolysis (1,3-dimethyl propylene carbonate rate 13.9 l. mole^{-1} min.$^{-1}$.)

The effect of methyl substitution on the solvolysis of succinic anhydride (IV) in water (see Table III) is to first increase and then decrease the rate. Here the five-membered ring will be nearly planar and the increase in the nonbonded interactions on replacing hydrogen atoms for methyl groups will increase ring strain and facilitate ring opening. Offset against this is the direct steric hindrance to approach of a nucleophile produced by methyl substituents and the accompanying increase in ring strain in going from a trigonal carbon atom to a four-coördinate atom in the transition state.[10] The corresponding five-mem-


IV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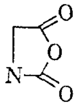
VI

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[8] N. L. Allinger and S.-E. Hu, *J. Am. Chem. Soc.*, **84**, 370 (1962).

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bered cyclic carbonates (V) all show considerable retardation in hydrolysis on substitution.[10] Substitution of the related N-carboxyglycine anhydrides (VI) also reduce their ease of hydrolysis by bases[12] and the retardation is particularly marked in the case of a bulky base, such as isopropylamine.

TABLE III

SOLVOLYSIS OF SUCCINIC ANHYDRIDES

	$k \times 10^5$ sec.$^{-1}$			
Anhydrides	40° H_2O[a]	40° EtOH[a]	35° pH 8.5, 28.5% EtOH—H_2O	0.4343 $k \times 10^4$, H_2O,[c] 25°
Succinic	746	2.02	570	692
Methyl	916	1.84	...	985
2,2-Dimethyl	...	...	350	...
Trimethyl	...	...	...	783
Tetramethyl	...	...	17	658

[a] Ref. 1c. [b] Ref. 1d. [c] Ref. 4b.

TABLE IV

PHYSICAL CONSTANTS OF GLUTARIC ANHYDRIDES

Anhydride	M.p., °C.	Lit. m.p., °C.
Glutaric	56 (b.p. 150/10 mm.)	56[a]
2-Methyl	(b.p. 95/7 mm.; n^{22}D 1.4622)	(b.p. 272–275)[b]
2,2-Dimethyl	37–38	38[c]
3-Methyl	41	41[d]
3,3-Dimethyl	124	124[e]
3-Ethyl-3-methyl	25	25[f]
3,3-Diethyl	(b.p. 126–127/8 mm.; n^{27}D 1.4650)	(b.p. 186–188/ 30 mm.)[f]

[a] See ref. 13. [b] A. Howles, T. Udall, and J. K. Thorpe, *J. Chem. Soc.*, 947 (1900). [c] J. C. Bardhan, S. K. Banerji, and M. K. Bose, *ibid.*, 1127 (1935). [d] F. V. Darbishire and J. K. Thorpe, *ibid.*, 1717 (1905). [e] A. S. Thorpe and J. K. Wood, *ibid.*, 1592 (1913). [f] B. Singh and J. K. Thorpe, *ibid.*, 117 (1923).

Experimental

Anhydrides.—Many of the substituted glutaric anhydrides were purchased from the Aldrich Chemical Company.

Glutaric anhydride and 3,3-diethylglutaric anhydride were prepared by refluxing the corresponding acids with acetic anhydride,[13] removing the excess by distillation at atmospheric pressure, and distilling the residue at reduced pressure.

2-Methylglutaric Anhydride.—Sodium methoxide (4.32 g.) was added to diethyl methylmalonate (18.0 g.) in benzene (100 ml.) containing dimethylformamide (30 ml.) The solution was stirred for 0.5 hr. and ethyl β-bromopropionate (15.0 g.) in benzene (25 ml.) added dropwise. The solution was refluxed for 14 hr. and worked up by adding water to give ethyl butane-2,2,4-tricarboxylate (11.3 g.), b.p. 125°/3 mm. n^{25}D 1.4680. This ester (5.8 g.) was refluxed for 8 hr. with sodium hydroxide (4.9 g.) in water (6.5 ml.), cooled in ice, and concentrated sulfuric acid (3.1 g.) in water (4.2 ml.) added. The solution was refluxed for 6 hr., cooled, and extracted continuously with ether. Distillation of the residue gave the anhydride (2.1 g.) b.p. 95°/7 mm., n^{25}D 1.4622.

The physical constants of the anhydrides are given in Table IV.

Solvent.—Dioxane was purified by refluxing and then fractionating from sodium.[14] Distilled water was taken from an all-metal still and contained in Pyrex vessels. The aqueous dioxane was prepared by mixing 5 vol. of distilled water with 1 vol. of purified dioxane.

Kinetics.—Samples of the anhydrides (0.1–1.5 g.) were dissolved in 1:5 dioxane–water (30 ml.) in a Pyrex tube, maintained at 0° in a bath of ice water, at 28.2 ± 0.1° in a constant temperature bath or in a bath of boiling acetone vapor at 56.7 ± 0.1°. The conductance of the solution was immediately measured using a dipping-type cell with platinized black electrodes, which fitted tightly into the Pyrex tube, and a Serfass conductivity bridge. Readings were taking at intervals up to 2–3 hr. and again after 24–48 hr. The rate constants were determined from the slope of straight line graphs of time against ln $(C_\infty - C_0)/(C_\infty - C_t)$, where C_∞, C_0, and C_t were the conductances at infinite, zero time, and time t. The runs were carried at least in triplicate and the mean values (mean error < 4%) are given in Table I.

Preliminary measurements in 3:1 and 1:4 dioxane–water gave rate constants for 3,3-dimethylglutaric anhydride at 28° of 5×10^{-6} and 1.5×10^{-4} sec.$^{-1}$, respectively. Since the first rate is very slow a solvent of composition 1:5 (v./v.) dioxane–water was chosen for the comparative study.

Acknowledgment.—This research was supported by grants from the National Science Foundation, the Organization of American States, and the Institute of International Education of the Department of State.

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