

The *gem* Effect. III. The Influence of 3-Mono- and 3-*gem* Substitution on the Acid Dissociation Constants of Glutaric Acid. A Comparison of the Sensitivity of ΔpK_a of Dicarboxylic Acids and the Rate of Ring Closure of Their Monoesters to the Intramolecular Distance Separating Carboxyl Functions

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The pK_1 and pK_2 values of a series of 13 3-mono- and 3-*gem*-substituted glutaric acids have been determined ($25 \pm 0.1^\circ$ in water). Increase in steric requirements of substituents decrease pK_1 and increase pK_2 . The effect of 3-monosubstitution on pK_1 and pK_2 was found to be negligible while that of 3-*gem* substitution was found to be great. A comparison of the pK_2 values (relative to glutaric acid) to the relative rates of ring closure of like-substituted mono-*p*-bromophenyl glutarate esters reveals that the $\log k_r$ of ring closure is 50-fold more sensitive to 3-monosubstitution while to *gem* substitution the $\log k_r$ for the ring closure reaction is but 1.5-fold more sensitive. These results find a rationale in the hypothesis that the steric effects on rotamer distribution in dicarboxylic acid and mono ester are essentially the same and that the ΔpK_a of glutaric acids are only directly related to the interprotonic distance when this distance is less than 5 Å. whereas the $\log k_r$ of the intramolecular reactions are directly related to the distance separating carboxyl anion and ester bond.

As the carboxyl groups of a dicarboxylic acid are brought into close proximity, the value of the first dissociation constant (K_1) increases while that of the second (K_2) decreases. For the aliphatic dicarboxylic acids this increase in ΔpK_a has been explained by considering electrostatic interactions as the primary factor³ and intramolecular hydrogen bonding⁴ as a secondary factor (electrostatic effects when mentioned will refer to effects other than hydrogen bonding). Thus, the equation of Kirkwood and Westheimer^{3b} for the calculation of the distances separating carboxyl groups from the known K_1 and K_2 values considers only electrostatic interactions. Intramolecular hydrogen bonding has been suggested to explain cases of non-agreement of the predictions of the Kirkwood–Westheimer^{3b} treatment though other factors as the assumed shape and internal dielectric constant of the molecule

should also be considered. Quantitative evaluation of the effect of hydrogen bonding obtained by comparing K_1 of dibasic acids with the ionization constant of the corresponding methyl ester for maleic acid ($\Delta pK_a = 4.42$)⁵ and some 2,3-disubstituted succinic acids ($\Delta pK_a \sim 4$)^{3e} in aqueous solutions suggests that for these acids internal hydrogen bonding may be a significant but not a dominating factor in determining K_2 . Spectral studies⁶ of the effects of hydrogen bonding for maleic acid and some alkylated aliphatic dibasic acids in aqueous solutions have indicated that intramolecular hydrogen bonding is unable to compete significantly with intermolecular hydrogen bonding to solvent. Only for those highly alkylated dicarboxylic acids in which the carboxyl groups are held in close proximity ($\Delta pK \gg 4$)^{3e} can internal hydrogen bonding become a dominant factor in determining the ratio of K_1/K_2 . Here the influence of hydrogen bonding has been shown only for the dissociation of the acid monoanion (for example, 2,3-*t*-butylsuccinic acid).^{3e} There is no evidence for hydrogen bonding in any of the protonated diacids so far investigated. It appears, then, that variations in K_1 are purely electrostatic. Dodd and co-workers have suggested^{6b} that the changes in K_1 for a series of unsubstituted aliphatic dibasic acids and their monoethyl esters is attributed to stronger dipole–dipole interactions between the carboxylic and ester groups as the distance separating them decreases.

Variations in K_1/K_2 for alkyl-substituted dibasic acids are obviously steric in origin. As the substitution of groups with increasing steric requirements brings carboxyl groups into closer proximity both electrostatic effects and intramolecular hydrogen bonding will increase. However, it is possible that the carboxyl groups could be forced into such close proximity that internal hydrogen bonding cannot be accommodated⁷ or that conformations of the carboxyl groups favoring

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

(3) (a) N. Bjerrum, *Z. physik. Chem.*, **106**, 219 (1923); (b) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506, 513 (1938); (c) F. H. Westheimer and M. Shookhoff, *J. Am. Chem. Soc.*, **61**, 555 (1939); (d) for a review see G. W. Wheland, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y. 1960, p. 515; (e) see also L. Ebersson, *Acta Chem. Scand.*, **13**, 211 (1959).

(4) (a) I. Jones and F. G. Soper, *J. Chem. Soc.*, 133 (1936); (b) L. Hunter, *Chem. Ind.* (London), 155 (1953); (c) H. C. Brown, *Science*, **118**, 370 (1953).

(5) (a) F. H. Westheimer and O. T. Benfey, *J. Am. Chem. Soc.*, **78**, 5309 (1956); (b) M. Levy and J. P. Magoulas, *ibid.*, **84**, 1345 (1962).

(6) (a) M. Shahat, *Acta Cryst.*, **5**, 765 (1952); (b) R. E. Dodd, K. E. Miller, and W. F. K. Wynne-Jones, *J. Chem. Soc.*, 2790 (1961); (c) for additional references see L. Ebersson, *Acta Chem. Scand.*, **17**, 1552 (1963); (d) D. Chapman, D. R. Lloyd, and R. H. Prince, *J. Chem. Soc.*, 550 (1964); (e) J. L. Haslam, E. M. Eyring, W. W. Epstein, G. A. Christiansen, and M. H. Miles, *J. Am. Chem. Soc.*, **87**, 1 (1965).

(7) See L. L. McCoy and G. W. Nachtigall, *ibid.*, **85**, 1321 (1963), for a study of 1,2-cyclopropanedicarboxylic acids where it is proposed that certain substituents in the 1,2-positions force the carboxyl groups too close together for effective hydrogen bonding, *i.e.*, the coplanarity needed for effective hydrogen bonding is hindered: G. C. Pimentel and A. L. McCellan, "Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, pp. 236, 265.

internal hydrogen bonding are hindered. High K_1/K_2 ratios in disubstituted malonic acids suggest, however, that large *gem* substituents bring about favorable carboxyl orientation for effective hydrogen bonding.⁸

Part III of this series deals with the determination of the influence of 3-mono- and 3-*gem* substitution on the pK_1 and pK_2 values for glutaric acid. The influence of substituents on rotamer distribution in glutaric acid are evaluated on the basis of the determined pK_a values. A comparison of the thermodynamic acidity constants with the kinetic constants for intramolecular nucleophilic attack in the solvolysis of 3-mono- and 3-*gem*-substituted mono-*p*-bromophenyl glutarate (see part II) allows further insight into the effect of substituents on the rotamer distribution in the monoesters.

Experimental Section

Materials. For preparation and procurement of the dicarboxylic acids, see part I.

Determination. The pK_a values were determined by titration employing a Radiometer TTT1b titrator equipped with a Radiometer PHA 630 Ta scale expander and a Radiometer SBR2c Titrigraph with a Radiometer SBU1a micrometer syringe drive which accommodated a 1-ml. Agla Trubore syringe which led to a three-neck \S Metrohm microtitration cell by way of a glass capillary. The glass capillary buret tip extended half-way into the solution to be titrated passing through an air-tight \S fitting. The other two necks of the microtitration vessel were fitted with a \S Metrohm-type X glass electrode and a \S salt bridge leading to an external calomel electrode. The tip of the \S salt bridge was fitted with an asbestos wick to prevent large changes in μ during the course of the titration. The cell (enclosed in a Faraday cage) had a 2-ml. capacity and was maintained at constant temperature by circulation of water through the water jacket from a Haake water bath which permitted temperature control at $25.0 \pm 0.1^\circ$. Carbonate-free base, 0.100 *N* potassium hydroxide, and 1.25×10^{-3} *M* carbon dioxide free aqueous acid solutions were used. Before titrating, the pH meter scale expander was standardized against buffer solutions at pH 4.00 and 7.00 and checked after titrating. Direct readings were taken from the micrometer arrangement (1.973×10^{-2} ml./div.) driving the Trubore syringe and from the scale expander. When $\Delta pK_a < 2.7$, the data were treated by Britton's modification of the method of Noyes for separating overlapping acidities^{9,10}; and when $\Delta pK_a > 2.7$ the data were treated by the method provided by Albert,¹⁰ the determination of the ionization constant of a monobasic acid requiring correction for the concentration of hydrogen ions. Corrections for liquid potentials and salt errors were not attempted. The titration technique and calculation method (Britton) were tested by titrating 1.25×10^{-3} *M* succinic acid. The result was pK_1 4.20 and pK_2 5.56 as compared with 4.20 and 5.60,¹¹ 4.22 and 5.67,¹²

(8) P. K. Glascoe and J. R. Hutchison, *J. Phys. Chem.*, **68**, 1562 (1964).

(9) H. Britton, "Hydrogen Ions," Chapman and Hall, London, 1955, p. 217; A. A. Noyes, *Z. physik. Chem. (Leipzig)*, **11**, 495 (1893).

(10) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 52.

(11) W. L. German and A. I. Vogel, *J. Am. Chem. Soc.*, **58**, 1546 (1936).

and 4.20 and 5.62,¹³ respectively. As a check on the purity as well as the authenticity of the runs, neutralization equivalents were calculated from the pH data and were generally within 1% of the correct value.

Results and Discussion

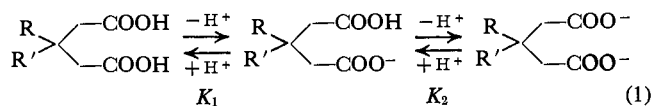
The acid dissociation constants for 3-mono- and 3-*gem*-substituted glutaric acids determined in this study are presented in Table I. From inspection of Table I

Table I. Tabulation of pK Data for 3-R,3-R'-Disubstituted Glutaric Acids

	R	R'	pK_1	pK_2	Log K_1/K_2	n^a
(a)	H	H	4.42 \pm 0.02	5.44 \pm 0.01	1.02	11
(b)	H	CH ₃	4.35 \pm 0.02	5.44 \pm 0.02	1.09	4
(c)	H	C ₆ H ₅	4.28 \pm 0.01	5.34 \pm 0.02	1.06	5
(d)	CH ₃	CH ₃	3.85 \pm 0.03	6.45 \pm 0.02	2.60	4
(e)	C ₆ H ₅	C ₆ H ₅	3.67 \pm 0.02	7.42 \pm 0.02	3.75	4
(f)	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	3.65 \pm 0.02	7.48 \pm 0.02	3.83	4
(g)	<i>i</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇	3.63 \pm 0.02	7.68 \pm 0.03	4.05	7
(h)	CH ₃	<i>i</i> -C ₃ H ₇	3.78 \pm 0.04	6.92 \pm 0.03	3.14	6
(i)	CH ₃	<i>t</i> -C ₄ H ₉	3.61 \pm 0.03	7.49 \pm 0.03	3.88	6
(j)	CH ₃	C ₆ H ₅	4.12 \pm 0.01	6.17 \pm 0.01	2.05	6
(k)	C ₆ H ₅	C ₆ H ₅	3.89 \pm 0.02	6.95 \pm 0.03	3.06	7
(l)	<i>n</i> -C ₃ H ₇	C ₆ H ₅	3.88 \pm 0.02	6.94 \pm 0.02	3.06	3
(m)	C ₆ H ₅	C ₆ H ₅	4.02 \pm 0.02	6.81 \pm 0.02	2.79	4
(n)	H	<i>n</i> -C ₃ H ₇	4.32	5.46	1.14	<i>b</i>
(o)	H	<i>i</i> -C ₃ H ₇	4.28	5.51	1.23	<i>b</i>

^a n = number of determinations. ^b G. Kortum, W. Vogel, and K. Adrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworth and Co. (Publishers) Ltd., London, 1961.

it is seen that *gem* substitution in the 3-position but not monosubstitution has a profound influence on both the first (K'_1) and second (K'_2) acid dissociation constants (eq. 1). Since the highest $\Delta pK'$ observed is 4.05, for $R = R' = i\text{-C}_3\text{H}_7$, intramolecular hydrogen bond-



ing will be considered as being of minor importance in influencing the acid dissociation (see Introduction).

In Figure 1 there is plotted $\log (K'_2/K'_{20})$ vs. $\log (K'_1/K'_{10})$ where subscript (0) refers to the constant for unsubstituted glutaric acid. Inspection of Figure 1 reveals that $\log (K'_1/K'_{10})$ and $\log (K'_2/K'_{20})$ are linearly related. From the slope of Figure 1 (*i.e.*, 2.86) it is apparent that substitution has a greater effect on K'_2 than K'_1 . This result is anticipated on the basis that forcing the carboxyl anion into proximity to an undissociated carboxyl group should have a greater electrostatic effect on K'_2 than forcing together two neutral carboxyl groups would have on K'_1 . For those acids possessing phenyl substituents the values of K'_1 are smaller and those of K'_2 greater than predicted from the size of the phenyl group (compare when $R = R' = \text{CH}_3$, $\log (K'_1/K'_{10}) = 0.57$, $\log (K'_2/K'_{20}) = -1.01$; with when $R = \text{CH}_3$, $R' = \text{C}_6\text{H}_5$, $\log (K'_1/K'_{10}) = 0.30$, $\log (K'_2/K'_{20}) = -0.73$). However, the K'_1 and K'_2 values for the phenylalkyl series and dialkyl series are still linearly related (Figure

(12) J. C. Speakman, *J. Chem. Soc.*, 855 (1940).

(13) H. S. Sims, *J. Am. Chem. Soc.*, **48**, 1251 (1926).

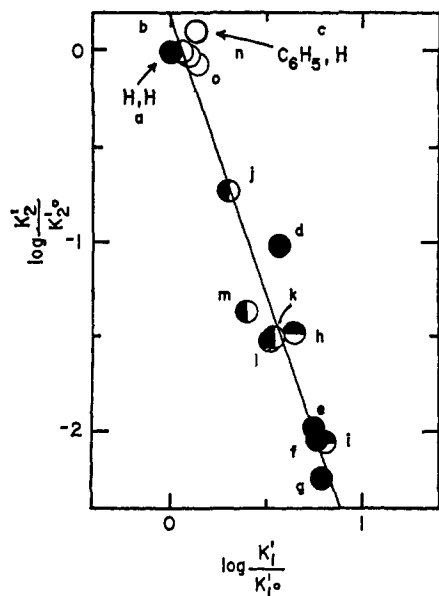
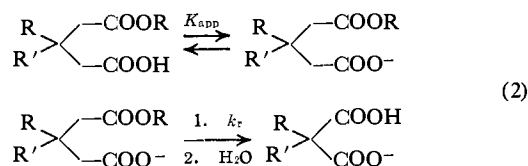


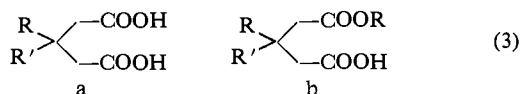
Figure 1. Correlation of $\log(K'_2/K'_{2o})$ vs. $\log(K'_1/K'_{1o})$: O, mono-substituted; ●, symmetrical dialkyl substituted; ◐, unsymmetrical dialkyl substituted; and ◑, phenylalkyl or diphenyl substituted glutaric acids.

1). The effect of the phenyl group is suggested to be due to dipole interaction of phenyl and carboxyl groups.^{3b}

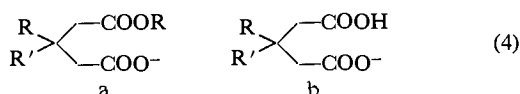
By combining the results obtained for the steric effect of 3-mono- and 3-*gem* substitution on the apparent acidities and the rates of ring closure of mono-*p*-bromophenyl glutarate (see part II) with the effect of like substitution on the acidities of glutaric acid there may be obtained information concerning the cause of the *gem* effect. For the ring closure reactions (see part II and eq. 2) steric effects on K_{app} may be related to



those on K'_1 and steric effects on k_r may be related to those on K'_2 . Thus, K'_1 and K_{app} both involve the electrostatic influence of a neutral species, undissociated carboxyl group and ester, respectively (eq. 3), on the



dissociation of a carboxyl group. If the preferred conformation of monoester and dicarboxylic acid are alike then the steric perturbation by like substituents on K_{app} and K'_1 would, *a priori*, be related. Both K_{app} and K'_1 are thermodynamic quantities and therefore dependent only on ground states. The relative values of both k_r and K'_2 are determined by the proximity of a carboxyl anion to a neutral species (eq. 4). Here we



compare a kinetic parameter to a thermodynamic parameter. If the conformation of ester and dicar-

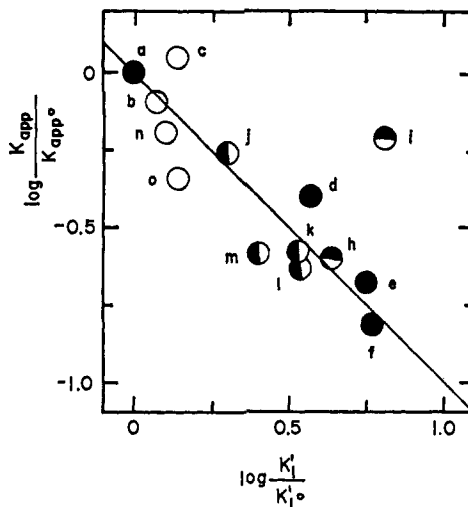


Figure 2. Correlation of $\log(K_{app}/K_{appo})$ vs. $\log(K'_1/K'_{1o})$ for 3-substituted glutaric acid monoesters and glutaric acids, respectively. The substitution pattern is indicated: O, monosubstitution; ●, symmetrical substitution; ◐, unsymmetrical dialkyl substitution; and ◑, phenylalkyl or diphenyl substitution.

boxylic acid are alike, a relationship between the changes of k_r and K'_2 with substitution might be anticipated providing that steric effects on k_r are determined only by alterations in the ground state of ester monoanion or in both ground state and transition state in a related manner. Changes in the ground state affecting K'_1 , K'_2 , K_{app} , and k_r brought about by 3-mono- and 3-*gem* substitution must be primarily on rotamer distribution.

In Figure 2 there is plotted $\log(K_{app}/K_{appo})$ vs. $\log(K'_1/K'_{1o})$. The changes in K_{app} and K'_1 with substitution are small so that it is difficult to obtain meaningful conclusions from Figure 2. The line of Figure 2 has been drawn as the best plot for the *gem*-substituted compounds. It may be noted that the slope of the plot of Figure 2 is -1.0 so that those points falling on the line represent cases where substituent effects have produced the same numerical change in the relative values of both dissociation constants although the changes are in opposite directions as anticipated from electrostatic effects.

Because of the greater perturbation of K'_2 and k_r by substitution, a plot of these two functions vs. each other (Figure 3) provides more information than the plot of K_{app} vs. K'_1 (Figure 2). Inspection of Figure 3 reveals that the points for mono- and *gem*-substituted compounds fall on two different plots. From the slopes of the lines of Figure 3 it is apparent that the sensitivity to monosubstitution on ring closure for ester monoanion is much greater than the sensitivity of monosubstitution on the dissociation constant of dicarboxylic acid monoanion. In fact, this greater sensitivity of ring closure to monosubstitution is also apparent when one compares K'_1 , K'_1/K'_2 , or the statistically corrected ΔpK_a (*i.e.*, $\log K_1/4K_2$) to k_r . The slope of the plot of Figure 3 for *gem*-substituted compounds is -1.5 , indicating that the rates of ring closure are only somewhat more sensitive than are the K'_2 values to *gem* substitution. On the other hand the slope for the monosubstituted compounds is -50 . Thus, substitution of a *n*- C_3H_7 group at the 3-position of glutaric acid changes K'_2 by but 1.05-fold

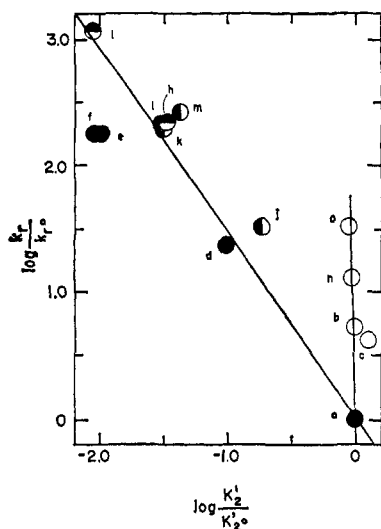


Figure 3. Correlation of $\log(k_r/k_r^0)$ vs. $\log(K'_2/K'_2^0)$ for 3-substituted glutaric acid monoesters and glutaric acids, respectively; substitution pattern: O, monosubstitution; ●, symmetrical substitution; ◐, unsymmetrical dialkyl substitution; and ◑, phenyl-alkyl or diphenyl substitution.

while the rate constant for *p*-bromophenol release from the anion of the monoester is increased by a factor of 12.9-fold. For 3-*gem* substitution by *n*-C₃H₇ K'_2 is changed by 109-fold and k_r by 179-fold. Monosubstitution clearly influences the rate of ring closure but scarcely the value of the acidity while *gem* substitution has a comparable influence on acidity and rate.

The effect on K'_2 of introducing nonpolar substituents at the 3-position must be ascribed to a change in rotamer population to favor conformations in which the carboxyl anion and carboxyl groups are in close proximity. The change in k_r on introduction of nonpolar substituents into the 3-position may also be due to a change of rotamer populations in the ground state or to a steric effect on the transition state(s).

That the large effect of monosubstituents on k_r is not due to a lowering of the transition state (particular to monosubstitution) is decisively shown by the fact that the $\log(k_r/k_0)$ values for *gem*-alkyl-substituted esters are simple additive functions of $\log(k_r/k_0)$ for the monosubstituted esters (see part II). Thus, k_r is not unusually sensitive to monosubstitution but K'_2 is unusually insensitive to monosubstitution and only *gem*-substitution significantly alters K'_2 ("the *gem* effect").

The effect of rotamer distribution on k_r has been decisively shown by Bruice and Pandit (Table II).^{14,15} From Table II it is seen that the freezing out of rotation about each single bond is associated with a rate increase of about 230-fold. In the 3,6-endoxo- Δ^4 -tetrahydrophthalate ester the reactant groups are eclipsed and the rate of intramolecular nucleophilic attack may be considered maximal [the $\log(k_r/k_r^0)$ value for the maleate ester in which bond angles are not as favorable as in 3,6-endoxo- Δ^4 -tetrahydrophthalate ester was found to be 4.02].¹⁵ The effect of mono- and *gem* substitution on the values of k_r of this

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

(15) T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960).

Table II. Relative Rates of Anhydride Formation from Monoester Anions

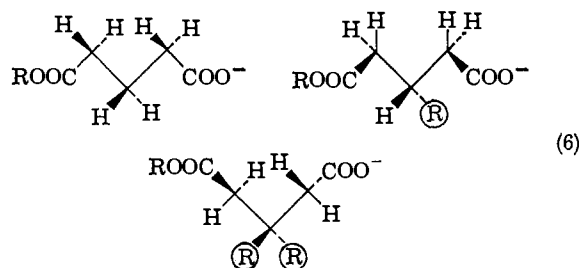
	$\log(k_r/k_r^0)$
	0
	2.37
	4.72

study must be due to the same freezing out of rotation about single bonds resulting in a decrease in the population of extended rotamers and thereby bringing the reactant ends statistically closer together. In the case of the 3-methyl-3-*t*-butylglutaric ester, the rate of ring closure [$\log(k_r/k_r^0) = 3.07$] approaches the limit of maximum acceleration obtained by fixing the reactant groups in an eclipsed conformation. It is anticipated that acceleration of rate due to the continued forcing of reactant groups into closer proximity will change gradually from a ground-state phenomenon attributed to decrease in extended rotamer populations to a transition state phenomenon attributed to relief of strain in the formation of the transition state. However, the latter should not be an important factor for the glutarate esters studied.

The influence of the juxtaposition of carboxyl groups on $\log(K_1/4K_2)$ for dicarboxylic acids has been examined by Westheimer and Shookhoff^{3c} employing the Kirkwood–Westheimer^{3b} equation (5). In eq. 5,

$$\log \frac{K_1}{4K_2} = \frac{e^2}{2.303kTRD_E} \quad (5)$$

e is the electrostatic charge, k is the Boltzman constant, T is the absolute temperature, R is the interprotonic distance, and D_E is an effective dielectric constant. In the study of Westheimer and Shookhoff the values of R (in Å.) were calculated for numerous dicarboxylic acids among which were three 3-mono- and four 3-*gem*-substituted glutaric acids. A plot of $1/R$ vs. $\log K_1/4K_2$ for these acids is not linear but possesses a negligible slope [*i.e.*, $(\log K_1/4K_2)/(1/R) \cong 4$] for the 3-mono-substituted acids but a large slope [*ca.* 75] for the *gem*-substituted acids. Employing the best curve to fit the points, the values of $1/R$ for the substituted glutaric acids of this study were interpolated and extrapolated. A plot of the so-determined values of R vs. $\log(k_r/k_0)$ for the ring closure reaction was found to be linear, fitting equally well the 3-mono- and 3-*gem*-substituted esters [$(\log k_r/k_0)/R \cong -1.0$]. We may assume the interprotonic distance (R) in the dicarboxylic acids to be directly related to the distance from carboxyl oxygen to ester carbonyl group in the monoesters. Allowing this assumption we may conclude that the $\log(k_r/k_0)$ of the ring closure reaction is a linear function of the distance separating the nucleophile and ester bond and that the effect of 3-mono- and 3-*gem* substitution is to decrease this distance by forcing the ends of the molecule into juxtaposition by nonbonded repulsion between substituent and reactant groups.



so that

$$\log k_r/k_0 \cong \frac{-R + 7.5}{\text{\AA}} \quad (7)$$

That the decrease in R , on monosubstitution in the 3-position, is not reflected in a change of ΔpK_a may be attributed to the only other variable in eq. 5, *i.e.*, D_E . The term D_E is a dielectric constant in name only, being a function of the shape of the molecule (for a spherical model the square of the ratio of the distance of the protons from the center of the sphere and the radius of the sphere), the dielectric constant of the molecule, and the dielectric constant of the solvent. The lack of sensitivity of ΔpK_a to changes in R on monosubstitution may be ascribed to an opposite and almost equal change in D_E . In unsubstituted glutaric

acid the electrostatic influence of carboxyl groups occur primarily through the low dielectric of the molecular backbone since, due to solvation of the polar carboxyl groups, the molecule exists in an extended conformation. Monosubstitution in the 3-position brings about a decrease in R accompanied by a greater fraction of the electrostatic effect occurring through the high dielectric of the solvent, and the decrease in R is matched by an increase in D_E so that the product of $D_E R$ in eq. 5 is not significantly altered. The conformational changes brought about by 3-*gem* substitution are greater than those brought about by the monosubstituents examined, and most of the electrostatic interaction occurs through the solvent so that D_E is essentially constant and the product of $R D_E$ becomes smaller with increasing steric requirements of the *gem* substituents.

By the reasoning presented above the similar influence of 3-*gem* substitution on $\log K_1/K_0$ and $\log k_r/k_0$ and the grossly greater sensitivity of $\log k_r/k_0$ to 3-monosubstitution is explained.

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Kinetics of Electron-Transfer Oxidation of Alkyl Radicals by Copper(II) Complexes

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Alkyl radicals are generated by the catalyzed decomposition of peroxides with Cu(II) complexes. They suffer oxidation to alkene by Cu(II) and reduction to alkane by a variety of hydrogen-donor substrates. The competitive formation of alkane and alkene has been utilized to evaluate the ratio of second-order rate constants for reduction and oxidation, k_h/k_e . Oxidation of alkyl radicals is half order in total Cu(II) species in glacial acetic acid and first order in aqueous acetic acid. Cupric acetate in glacial acetic acid is highly dimerized, but the dissociation constant can be determined kinetically. Water, pyridine, and acetate ions effect dissociation of the dimer. Only the monomeric Cu(II) entities are effective oxidants, the dimer of cupric acetate being inactive. The effect of altering the Cu(II) species on oxidation is discussed. By extrapolating values of hydrogen-transfer rates obtained in the gas phase to solution, it is possible to estimate the absolute rates of oxidation of alkyl radicals by Cu(II) complexes. These rates approach the diffusion-controlled limit. They are compared qualitatively with other facile "outer sphere" reactions of inorganic ions in the light of Marcus' theory of electron transfer.

Introduction

A sizeable body of qualitative information has accumulated concerning the oxidation and reduction of organic free radicals by metal salts. Among metal oxidants, Cu(II), Pb(IV), Fe(III), and Co(III) have been those best studied. At least two mechanisms have been described for the oxidation of carbon-centered free radicals by Cu(II) compounds; these are ligand transfer¹ and electron transfer.² The qualitative difference between these two modes of oxidation has been delineated.³

The importance of these reactions lies in their rapid rates, such that they can be utilized in synthetic schemes involving reactive free radicals.⁴ However, quanti-

(1) (a) C. H. Bamford, A. Jenkins, and R. Johnston, *Proc. Roy. Soc. (London)*, **A239**, 214 (1957); (b) J. K. Kochi, *J. Am. Chem. Soc.*, **78**, 4815 (1956); **79**, 2942 (1957); **84**, 2124 (1962); (c) J. Kumamoto, H. De La Mare, and F. F. Rust, *ibid.*, **82**, 1935 (1960).

(2) (a) E. Collinson, F. S. Dainton, D. R. Smith, G. J. Trudel, and S. Tazuke, *Discussions Faraday Soc.*, **29**, 188 (1960); (b) H. E. De La Mare, J. K. Kochi, and F. F. Rust, *J. Am. Chem. Soc.*, **85**, 1437 (1963).

(3) J. K. Kochi, *Tetrahedron*, **18**, 483 (1962).

(4) J. K. Kochi, *J. Am. Chem. Soc.*, **84**, 774, 1572, 2121, 2785 (1962); G. Sosnovsky and S. O. Lawesson, *Angew. Chem. Intern. Ed. Engl.*, **3**, 269 (1964).