The *gem* Effect. II. The Influence of 3-Mono- and 3,3-Disubstitution on the Rates of Solvolysis of Mono-*p*-bromophenyl Glutarate

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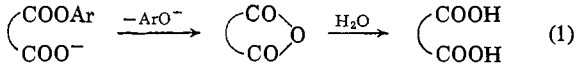
The influence of 3-mono- and 3-gem substitution of alkyl and aryl groups on the rate constant (k_r) for ester solvolysis via carboxyl anion participation and on the kinetically determined pK'_{app} values of mono-p-bromophenyl glutarate have been determined. Both the k_r and pK_{app} values increase with the effective bulk of the substituent groups as anticipated from the greater statistical proximity of carboxyl and ester functional groups. The kinetic effect of gem substitution tends to be an additive function calculable from the kinetic effect brought about by monosubstitution (i.e., gem substitution does not increase the bulk effect of substituent groups). The phenyl group, in all instances, exhibits a much smaller steric effect than anticipated from its known size and steric effect in other systems. This has been suggested to be due to hydrophobic backbinding of the phenyl substituent with the ester p-bromophenoxy group so as to increase the population of nonprofitable extended rotamers.

Introduction

The solvolysis of monophenyl esters of dicarboxylic acids has been shown to proceed through intermediate formation of anhydride.[3] Thus, in the case of sub-



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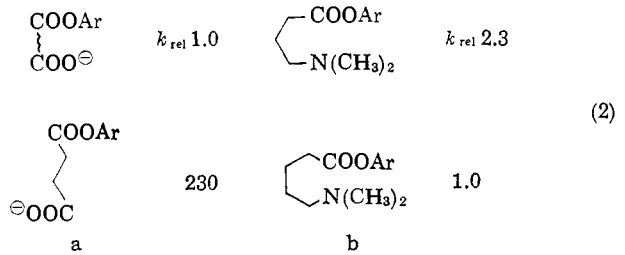
stituted phenyl esters of maleic acid, 3,6-endoxo-Δ^4-tetrahydrophthalic acid,[3a] and phthalic acid,[3c] anhydride can be shown kinetically to be an intermediate. The rate of phenolate ion release is markedly dependent on the distance between carboxyl anion and ester group which has led to the suggestion that, in aqueous solution, the mono esters exist in an extended conforma-



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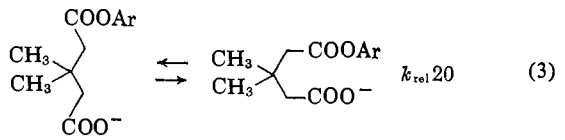
a b

tion.[2a,3,4] In the solvolysis of the 4-dimethylaminoalkylcarbophenoxy esters, the relative rates of attack of the dimethylamino group on the ester bond suggest that the preferred conformation, in aqueous solution, is one of close approach of reacting groups (eq. 2b). The enhancement in the rates of solvolysis of the monoaryl esters of glutaric acid brought about by 3-mono- and 3-*gem* substitution has been suggested[3] to be due to a decrease in the kinetically unprofitable extended rotamer population (eq. 3). Due to the



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sensitivity of the rate of intramolecular nucleophilic attack on substituent effects the 3,3-disubstituted monoesters of glutaric acid are particularly suitable to the study of the *gem* effect. In this paper we report our studies on the effect of 3- and 3,3-disubstitution of alkyl and phenyl groups on the rate of solvolysis of the mono-*p*-bromophenyl ester of glutaric acid. These studies have been carried out at 30° in 50% (v./v.) dioxane–water solution of μ = 0.65 (with KCl).

Experimental Section

Compounds. The sodium salts of the 3-substituted monophenyl esters of glutaric acids were prepared from their corresponding analytically pure anhydrides (see part I). To an ether solution of *p*-bromophenol was added an equimolar amount of sodium.[3] The suspension was stirred until all the sodium reacted. To an ether solution of anhydride was added enough phenoxide solution to precipitate a sufficient amount of the ester salt. Reaction time ranged from 12 to 96 hr. depending on the difficulty of anhydride opening. Sodium-dried ether was used and all reactions were kept under nitrogen. The sodium salts of the monoesters were collected by filtration, washed with sodium-dried ether, and dried under vacuum.

Apparatus. A Zeiss PMQ II spectrophotometer equipped with a thermostated brass cuvette holder, through which was circulated water of constant temperature (30.0 + 0.1°), was used for kinetic measurements. All pH measurements were made with a Radiometer Model 22 pH meter with a Radiometer Model PHA 630 Pa scale expander. The combined glass–calomel electrode (Radiometer G. K. 2021C) and electrode cell compartment were thermostated at the reaction temperature.

Kinetic Measurements. An approximate volume of solution B (30°) was added to either a 2- or 3-ml. cuvette and thermostated in a brass cuvette holder for 10–15 min. At the same time an approximate (solution A, 0.65 *M* KCl, 0.05 *M* NaOAc in 50% dioxane–

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

(3) (a) T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960); (b) L. Eberson, *Acta Chem. Scand.*, **16**, 2245 (1962); (c) T. C. Bruice and J. Thanassi, unpublished results.

(4) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, **85**, 1 (1963).

Table I. Rate Data for the Hydrolysis of Mono-*p*-bromophenyl Esters of 3,3-R,R′-Glutaric Acids (30°, μ = 0.65 *M* KCl, 50% Dioxane–Water (v./v.))

pH	10^2k_{obsd}, min.$^{-1}$	10^2k_r, min.$^{-1}$	pK_{app}	r^a
(a) R = R′ = H				
5.67	0.119			
5.98	0.168			
6.17	0.214			
6.46	0.261			
6.50	0.264			
6.58	0.290			
6.66	0.274			
6.74	0.283			
6.78	0.302	0.339 ± 0.03	5.95 ± 0.02	0.99
(b) R = H, R′ = CH_3				
5.70	0.501			
5.82	0.606			
6.01	0.782			
6.24	1.015			
6.50	1.18			
6.91	1.43	1.62 ± 0.01	6.04 ± 0.02	1.00
(c) R = H, R′ = C_3H_7				
5.66	1.07			
5.84	1.50			
5.99	1.85			
6.09	1.91			
6.34	2.69			
6.45	2.95			
6.68	3.37			
6.88	3.68			
6.88	3.79	4.38 ± 0.05	6.14 ± 0.03	0.99
(d) R = H, R′ = *i*-C_3H_7				
5.66	2.18			
5.97	3.71			
6.20	4.99			
6.71	8.00			
6.85	9.20	11.33 ± 0.15	6.29 ± 0.03	1.00
(e) R = H, R′ = C_6H_5				
6.16	0.898			
6.36	0.987			
6.48	1.12			
6.51	1.15			
6.66	1.19			
6.77	1.20			
6.87	1.26	1.39 ± 0.02	5.90 ± 0.06	0.97
(f) R = CH_3, R′ = C_6H_5				
5.47	1.70			
5.50	1.74			
5.68	2.55			
5.69	2.52			
5.99	4.05			
5.99	4.16			
6.23	5.60			
6.39	6.83			
6.47	6.86			
6.73	8.41	10.94 ± 0.07	6.21 ± 0.02	0.99
(g) R = C_2H_5, R′ = C_6H_5				
5.46	5.75			
5.72	10.26			
5.98	15.70			
6.22	24.80			
6.23	23.00			
6.75	45.60			
6.96	54.4	72.8 ± 0.9	6.53 ± 0.03	0.99
(h) R = *n*-C_3H_7, R′ = C_6H_5				
5.31	3.22			
5.56	5.29			
5.83	10.40			
6.09	15.9			
6.43	31.0			
6.51	30.7			
6.80	38.6			
6.89	46.4	67.8 ± 1.8	6.59 ± 0.05	0.96
(i) R = R′ = CH_3				
5.98	2.36			
6.21	3.33			
6.51	4.72			
6.77	5.67			
6.97	6.33	7.83 ± 0.07	6.34 ± 0.01	1.00
(j) R = R′ = C_2H_5				
5.51	4.48			
5.75	6.77			
6.01	11.5			
6.25	16.9			
6.56	27.2			
6.76	35.7			
6.92	40.7	60.6 ± 1.0	6.63 ± 0.03	0.99
(k) R = R′ = *n*-C_3H_7				
5.26	1.76			
5.48	3.08			
5.97	8.50			
6.19	11.6			
6.24	13.9			
6.39	17.7			
6.47	20.3			
6.60	26.6			
6.72	30.4			
6.74	27.6			
6.77	30.5			
6.82	32.4	60.5 ± 0.9	6.77 ± 0.04	0.97
(l) R = R′ = C_6H_5				
5.39	6.14			
5.45	7.02			
5.74	12.27			
6.00	20.0			
6.21	28.3			
6.46	43.0			
6.72	53.0			
6.91	66.7	91.7 ± 1.1	6.54 ± 0.02	0.99
(m) R = CH_3, R′ = *i*-C_3H_7				
5.28	3.84			
5.59	7.46			
5.80	11.0			
6.06	17.6			
6.41	31.5			
6.63	38.3			
6.86	52.9	74.6 ± 1.2	6.55 ± 0.03	0.99
(n) R = CH_3, R′ = *t*-C_4H_9				
4.94	20.8			
5.15	31.1			
5.26	41.1			
5.52	66.3			
5.79	106			
5.79	113			
5.82	104			
5.83	106			
6.09	179			
6.22	204			
6.36	214	359 ± 6	6.16 ± 0.04	0.96
(o) R = R′ = *i*-C_3H_7[b]	(455)		(6.42)	

[a] Correlation coefficient. [b] Difficulty in reacting the anhydride with sodium *p*-bromophenoxide yielded a monoester salt that was so impure with phenoxide that only very approximate kinetic data could be calculated from the changes in O.D. observed spectrophotometrically.

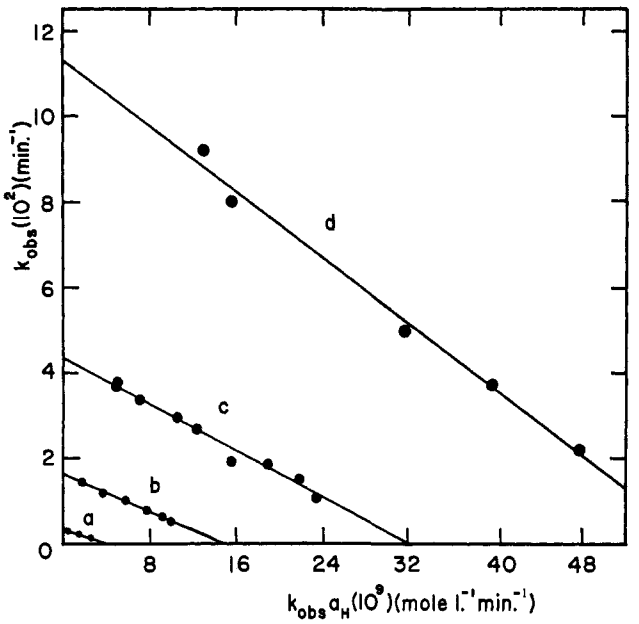
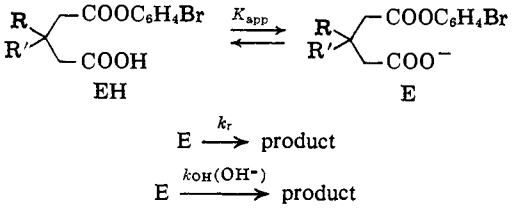


Figure 1. Examples of the Eadie plots of k_{obsd} *vs.* $k_{obsd}a_H$ from which k_r (intercept) and $1/K_{app}$ (slope) can be determined for the solvolysis of the mono-*p*-bromophenyl esters of 3,3-R,R′-disubstituted glutaric acids: (a) R = R′ = H; (b) R = H, R′ = CH_3; (c) R = H, R′ = *n*-C_3H_7; (d) R = H, R′ = *i*-C_3H_7.

water (v./v.); solution B, 0.65 *M* KCl, 0.05 *M* HOAc in 50% dioxane–water (v./v.)) volume of solution A in a 2-ml. capacity glass hypodermic syringe which was fitted with a polyethylene needle was thermostated in a brass syringe holder. After equilibrating at 30° a few grains of the sodium salt of the monoester was added to the cuvette containing solution B. The cuvette was capped and carefully shaken until solution was complete, then solution A from the syringe was added, the solution was mixed, and the cuvette was placed in the thermostated holder in the Zeiss and the change in optical density measured against time. Solution B was employed as a blank. The increase in *p*-bromophenoxide absorbance was measured at 280 mμ. At the completion of the kinetic run the pH was measured. Over a pH range of 5.00 to 7.00 the pH drift from beginning to end of a kinetic run was generally no more than ±0.02. The pseudo-first-order rate constants were determined by the method of Guggenheim.[5]

Results

From previous experience[3] it was anticipated that the solvolysis of the mono-*p*-bromophenyl glutarate esters would follow the scheme of eq. 4. In the pH



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range employed the term $k_{OH}(E)(OH^-)$ is not important so that the appearance of *p*-bromophenolate ion can be expressed kinetically as eq. 5.

$$\frac{d(P)}{dt} = \frac{(k_r K_{app})E_T}{(K_{app} + a_H)} \quad (5)$$

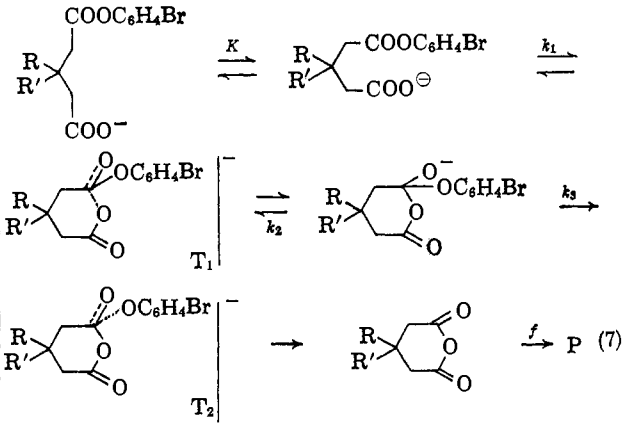
where E_T is the total ester concentration ($E_T = E + EH$), K_{app} is the kinetically apparent acid dissociation constant for the carboxyl group, and a_H is the hydrogen ion activity as determined with the glass electrode. At constant pH, the pseudo-first-order rate constant (k_{obsd}) for appearance of *p*-bromophenolate ion is provided by eq. 6. Plots of k_{obsd} *vs.* $k_{obsd}a_H$ in all

$$k_{obsd} = k_r \frac{K_{app}}{(K_{app} + a_H)}$$
$$k_{obsd} = K_r - \frac{k_{obsd}a_H}{K_{app}} \quad (6)$$

cases were linear (see Figure 1 for some examples), indicating that in the pH range considered OH^- catalysis of hydrolysis was negligible. From plots of k_{obsd} *vs.* $k_{obsd}a_H$ the values of k_r were obtained as intercepts and $1/K_{app}$ as slopes. The values of k_{obsd}, pH, k_r, and pK_{app} for all the esters studied are provided in Table I. For the evaluation of k_r and K_{app} the method of least squares was employed.[6]

Discussion

To ascertain the possible steric effect of 3-substituents on the rate of intramolecular nucleophilic catalysis of the hydrolysis of mono-*p*-bromophenylglutarate attention is called to eq. 7. The kinetic



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equation of (8) would pertain to eq. 7. In eq. 7 and

$$k_r = \frac{(Kk_1)}{\alpha + 1}, \qquad \alpha = k_2/k_3 \quad (8)$$

8 *K* represents a coefficient for the mole fraction of monoester anion existing in a reactive conformation with carboxyl anion and ester function in close proximity. Increase in the bulk of R and R′ should decrease the volume in which the reactive ends of the molecule can exist and increase *K*. Therefore, increase in the size of R should increase the rate of nucleophilic attack (Kk_1).

The data collected in this study are in good agreement with that little data which have been reported in the literature summarized in Table II. Inspection of Table II reveals that the relative rate constants for cyclization of 2-substituted 4-bromobutylamines obtained by Brown and van Gulick[7] follow the same order

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

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

Table II. Comparison of Experimental Logarithms of Relative Rate Data with Pertinent Literature Data

R	R′	3-Substituted mono-*p*-bromophenyl glutarates Exptl.[a]	Lit.[b]	2-Substituted 4-bromobutylamines[7]
H	H	0	0	0
CH_3	H	0.66	0.64	...
C_6H_5	H	0.60	0.53	...
CH_3	CH_3	1.35	1.29	2.20
C_2H_5	C_2H_5	2.25	...	2.77
C_6H_5	C_6H_5	2.42	...	3.72
i-C_3H_7	i-C_3H_7	3.1	...	3.96

[a] Rate data from Table I relative to where R = R′ = H. [b] See ref. 3a.

of rate enhancement and are of the same order of magnitude as the rate enhancements determined in this study. Since the displacement of Br^- by an amino functional group must be an SN2 reaction without intermediate formation it follows that the steric effect of geminal substitution must be on Kk_1 rather than on α in eq. 8. Inspection of Stuart–Briegleb models suggests that no real relief of strain should accompany the k_1 step so that the effect of 3-substitution should be on K (eq. 7).

It is interesting to note that there appears to be a trend toward additivity among the logarithms of the relative rates of solvolysis for the monophenyl esters employing the log k_{rel}, where $k_{rel} = k_r/k_{r^0}$, for substrates in which R = H and R′ = alkyl or phenyl as references (Table III). For R = H and R′ =

Table III

R′	R	Log k_{rel}
H	H	0.00
CH_3	H	0.721
C_6H_5	H	0.621 (0.786) (1.216)
n-C_3H_7	H	1.110
i-C_3H_7	H	1.521
C_2H_5	H	(1.126
t-C_4H_9	H	(2.34)

C_6H_5 the log k_{rel} value of 0.621 was obtained experimentally, the value of 0.786 was obtained as the difference between log k_{rel} for R = C_6H_5, R′ = CH_3 and log k_{rel} for R = H, R′ = CH_3. For R = H and R′ = C_2H_5 the value of log k_{rel} was assumed to be equal to 0.5 log k_{rel} for when R = R′ = C_2H_5 since an experimental value of log k_{rel} for R = H and R′ = C_2H_5 was not obtained. The value of log k_{rel} for R = t-C_4H_9 and R′ = H was obtained as the difference of log k_{rel} value when R = t-C_4H_9, R′ = CH_3 and R = H and R′ = CH_3. Employing the log k_{rel} values listed above one may calculate the steric effect of functional groups. Thus, for R = CH_3 and R′ = i-C_3H_7, log k_{rel} is calculated as the sum of log k_{rel} values for R = CH_3, R′ = H and R = i-C_3H_7, R′ = H. The calculated values are compared to the experimentally determined values for alkyl substituents in Table IV. It would appear as though the

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

Table IV

R	R′	Log k_{rel} Exptl.	Calcd.	Δ
CH_3	CH_3	1.36	1.44	0.08
n-C_3H_7	n-C_3H_7	2.25	2.22	0.03
i-C_3H_7	i-C_3H_7	3.13	3.04	0.09
CH_3	i-C_3H_7	2.34	2.24	0.10

phenyl group does not exert a constant steric effect. In the case of R = C_6H_5 a small steric effect (log k_{rel} = 0.621 to 0.786) is encountered when R′ = H or CH_3 and a larger effect (log k_{rel} = 1.216) is observed when substituents larger than methyl are employed with a phenyl substituent. Employing these values the following comparisons may be made (Table V).

Table V

R	R′	Log (k_r/k_{r^0}) Exptl.	Calcd.	Δ
C_6H_5	CH_3	1.51	1.34–1.51	0–0.17
C_6H_5	C_2H_5	2.33	2.34	0.01
C_6H_5	n-C_3H_7	2.30	2.33	0.03
C_6H_5	C_6H_5	2.43	2.43	0

The two additive values that must be employed for the C_6H_5 substituent may be related to its tendency to form hydrophobic bonds with the *p*-bromophenyl ester function. This would suffice to extend the monoester molecule and thus slow down the rate of ring closure. This factor will be considered later. Because of the apparent similarity in the rate constants for the solvolysis of the diethyl and di-*n*-propyl esters and the similarity between the rates of solvolysis for phenylethyl and phenyl-*n*-propyl substituted esters, chain lengthening to the extent of one additional carbon beyond ethyl has no significant effect on the rate constants. But chain branching has quite a significant effect. For R = H, R′ = CH_3 or R = R′ = CH_3, replacement of each hydrogen on one of the methyl groups by methyl increases log k_{rel} by 0.50 ± 0.09.

The rates of the ring closure reaction can be shown to be insensitive to polar effects but sensitive to the effective size of the substituent groups. Not only are the polar effects small for alkyl substituents but the substituents are removed by two carbons from the ester and nucleophilic carboxyl group. Most important, however, is the fact that the nucleophilicity of the carboxyl anion group and the susceptibility of the ester bond to nucleophilic attack should be oppositely influenced by electronic effects and, therefore, electronic effects should cancel out. In Figure 2 there is plotted the log k_{rel} values for this study *vs.* the steric substituent constants of Taft.[8] In Figure 2, the E_S scale has been shifted to give hydrogen a value of 0. The linear plot of Figure 2 was drawn by least squares; the steric reaction constant δ equals −0.83 ± 0.08 (correlation coefficient[8] of 0.95). The value of δ is of the same size as that obtained for the steric effect of substituents at the 3-position on the rate of hydrolysis of glutaric anhydride (δ = +0.90; see part I) but of opposite sign,

(8) 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. 598.

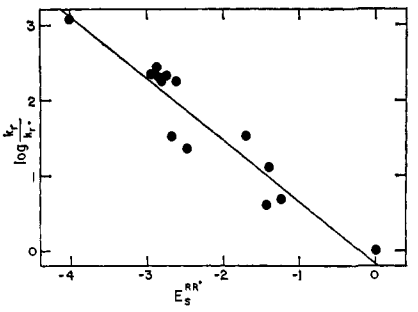


Figure 2. Plot of log (k_r/k_{r0}) *vs.* $E_S^{RR'}$ correlating the relative rate of ring closure with Taft's steric substituent constants.

indicating that increasing steric bulk has an acceleration on rate.

The kinetically determined apparent ionization constants (K_{app}) of the nucleophilic carboxyl group, as derived from eq. 4, 5, and 6, generally decrease as the steric bulk of the substituents increase (Table I). Similar trends have been noted for the titrimetrically determined K_a values for the monoesters of substituted malonic and succinic acids.[9] Exceptions, noted in this study, are for the most sterically hindered esters (*i.e.*, R = R′ = *i*-C_3H_7 and R = CH_3, R′ = *t*-C_4H_9). With the two exceptions noted, the log k_{rel} values are linearly related (Figure 3) to log (K_{app}/K_{app^0}) where K_{app^0} is the K_{app} for the unsubstituted glutarate ester. The slope of the least-squares line of Figure 3 is -2.71 ± 0.28 ($r = 0.94$), indicating the rate constants to be about 500 times more sensitive to the effect of 3-substitution than the K_{app} values. The increase in pK_{app} accompanying the increase of steric requirements of 3-substituents may be ascribed to a greater statistical abundance of rotamer conformations favoring electrostatic interaction. The correlation coefficient of 0.94 is good for the plot of Figure 3 when one considers that polar effects should be of significance in determining the pK_{app} values but not in the log k_{rel} values.

It is interesting to note the obviously anomalous high K_{app} and low k_r values for 3-phenylglutarate when one considers that the effective size of the phenyl group might be expected to compare with that of the isopropyl group (see Figure 3 and Table I). The K_{app} values generally decrease as the bulk of the monosubstituent increases until for R′ = *i*-C_3H_7, R = H, log $(K_{app}/K_{app^0}) = -0.35$ while for R′ = C_6H_5, R = H, log $(K_{app}/K_{app^0}) = +0.05$. That the 3-phenylglutarate may even be a stronger acid than the unsubstituted monoester suggests that the phenyl group contributes a much smaller steric effect than it should from bulk considerations alone. Although a polar inductive effect leading also to reduced electrostatic interaction could account for a significant part of the deviation, it may not account for all of the deviation observed in

(9) T. C. Bruice and W. C. Bradbury, *J. Am. Chem. Soc.*, **87**, 4838 (1965); M. Levy and J. P. Magoulas, *ibid.*, **84**, 1345 (1962); L. Eberson, *Acta Chem. Scand.*, **13**, 211 (1959).

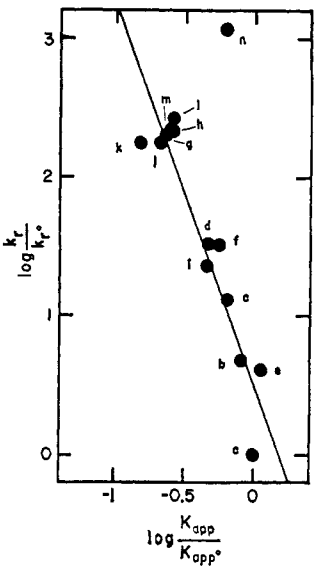
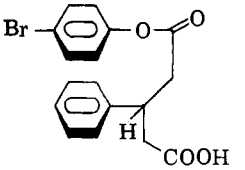


Figure 3. Plot of log (k_r/k_r^0) *vs.* (K_{app}/K_{app^0}) correlating the rates of ring closure with the change in the apparent ionization constants. (See Table I for letter keys.)

Figure 3. Most certainly the reduction in the rate of ring closure cannot alone be a result of the above polar effect. We wish to suggest that the introduction of a 3-phenyl substituent provides a site for hydrophobic bonding[10] with the phenyl ring of the ester group shown. Such a tendency would increase the



population of extended conformations and reduce the population of closed forms accordingly. The statistical average of the population of conformers is suggestively close to that for glutarate or 3-methylglutarate with the polar effects causing additional deviation. 3-Phenyl-3-alkyl substitution most probably causes compensatory effects on K_{app} between hydrophobic bonding of the phenyl rings and polar effects increasing the acidity of the protonated monoester, and steric compression causing a greater population of closed forms which increases the electrostatic interaction and thereby decreases the acidity of the protonated monoester. The rate data (see Table I) suggests a greater acidity (K_{app}) and slower rate (k_r) than to be anticipated if closed conformations were as predominant as expected from the bulk interactions of the phenyl and alkyl groups with the carboxyl and carbophenoxy groups.

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

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