The Effect of Carboxyl Groups in Neighboring Side Chains on the Hydrolysis of Substituted Benzyl and Fluorenyl Bromides

LEROY CHAUFFE, L. J. ANDREWS, AND R. M. KEEFER

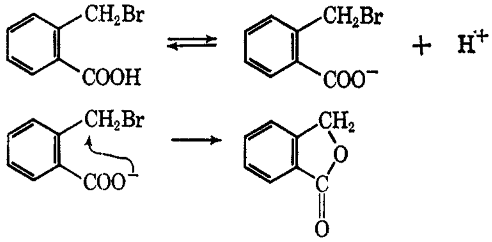
The Department of Chemistry, University of California, Davis, California 95616

Received May 12, 1966

A study has been conducted of the capacity of COOH and COO^- groups in neighboring side chains to participate in the hydrolysis of certain substituted benzyl and 9-fluorenyl bromides in aqueous dioxane. Both *o*-carboxybenzyl bromide and its sodium salt are much more reactive than their *para* isomers. Their high reactivities are ascribed to internal participation of the carboxyl and carboxylate groups, respectively, as an electrophile and nucleophile. The reaction of *o*-carboxybenzyl bromide itself does not proceed by way of the anion, $BrCH_2C_6H_4COO^-$, since the reaction rate is not depressed by added hydrogen bromide. The *ortho* and *para* isomers of bromomethylphenylacetic acid (and also of their methyl esters) are comparable in reactivity as are also the 9-bromofluorene-1- and -4-carboxylic acids and the 9-bromofluorene-1- and -4-acetic acids. Apparently participation by the *ortho* substituents (or the 1 substituents in the fluorene derivatives) does not occur in these reactions. Evidence has, however, been obtained of *o*-COO^- participation in the reactions of the sodium salts of *o*-bromomethylphenylacetic and 9-bromofluorene-1-carboxylic acid but not in the reaction of 9-bromofluorene-1-acetic acid. Neither does it appear that the hydrolysis of 3-(*o*-bromomethyl)phenylpropionic acid is accompanied by carboxyl participation. These observations are discussed in terms of the molecular geometries of the various bromo acids.

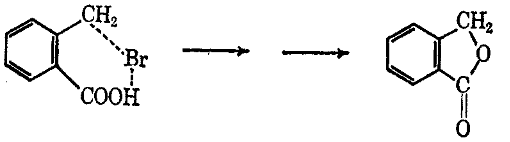
The fact that *o*-carboxybenzyl bromide hydrolyzes much faster than its *para* isomer has been explained on the assumption that the *o*-COOH substituent participates in the displacement process.[1]

The possibility that this group participates as a nucleophile through attack of one of its oxygens on the carbon at the reaction center is regarded as improbable.[1] In this connection it is significant that *o*-carbomethoxybenzyl bromide, in which the $COOCH_3$ group is also functionally constituted to serve as a nucleophile, does not in fact hydrolyze much more readily than *p*-carbomethoxybenzyl bromide.[1,2] It is conceivable that the high reactivity of *o*-carboxybenzyl bromide might be traced to rapid internal displacement of bromide from the anion of the acid, which must be present in the medium in low concentration during the course of the hydrolysis (eq 1).



(1)

As later demonstrated this pathway is not a likely one since the rate of hydrolysis of the bromide is not markedly affected by added hydrogen bromide. It is, therefore, currently regarded as most likely that in the hydrolysis of *o*-carboxybenzyl bromide cleavage of the C-Br bond is facilitated through participation of the carboxyl group as an electrophile (eq 2); that is rupture of this bond is promoted through internal hydrogen bonding.



(2)

In previous investigations of nucleophilic participation by substituents in aromatic side chains on reactions at adjacent side chains, it has been shown that relatively minor changes in the placement of the substituents may have a profound effect on their contribution to reactivity.[3] For example the carbomethoxy group promotes dissociation of *o*-$CH_3OOCC_6H_4ICl_2$ far more effectively than it does in the corresponding reaction of *o*-$CH_3OOCCH_2C_6H_4ICl_2$.[3b]

It has seemed of interest to assess the importance of geometry as a factor relating to the capacity of a carboxyl group in a nearby side chain to participate in the hydrolysis of substituted benzyl bromides. A kinetic investigation has now been conducted of the reactions in aqueous dioxane of a number of bromo acids of interest (and certain of their salts), including *o*- and *p*-bromomethylphenylacetic acids, 3-(*o*-bromomethyl)phenylpropionic acid, 9-bromofluorene-1- and -4-carboxylic acids, and 9-bromofluorene-1- and -4-acetic acids. Earlier work on the hydrolysis of *o*- and *p*-carboxybenzyl bromides has been extended and a comparison of the hydrolysis rates of methyl *o*- and *p*-bromomethylphenylacetic acids has been made as an incidental matter.

Experimental Section

_o_- and _p_-Carboxybenzyl Bromides.—The isomeric bromo acids were prepared by the procedure employed previously.[1]

_o_- and _p_-Tolylacetic Acids.—A mixture of 89 g of N-bromosuccinimide, 0.1 g of benzoyl peroxide, and 53 g of *o*-xylene in carbon tetrachloride was heated at reflux for 4 hr. The mixture was filtered, and 50 g (54% yield) of *o*-methylbenzyl bromide (bp 220–225°) was recovered from the filtrate by distillation at atmospheric pressure. This bromide was converted to *o*-methylbenzyl cyanide and the latter to *o*-methylphenylacetic acid by established methods.[4] The product melted at 87.5–88.5° (lit.[4] mp 88–89°). This and other melting points which are reported

---

[1] A. Singh, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 1179 (1962).

[2] It is recognized that, in solvolytic reactions of certain organic halides, carbonyl and carboxyl groups which are substituted gamma to the reaction center may participate intramolecularly as nucleophiles; see, for example (a) L. I. Smith and J. R. Holum, *ibid.*, **78**, 3417 (1956); (b) S. Oae, *ibid.*, **78**, 4030 (1956); (c) G. Baddeley, E. K. Baylis, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc.*, 451 (1961); (d) D. J. Pasto and M. P. Serve, *J. Am. Chem. Soc.*, **87**, 1515 (1965).

[3] (a) R. E. Lovins, L. J. Andrews, and R. M. Keefer, *ibid.*, **84**, 3959 (1962); (b) L. J. Andrews, L. Spears, and R. M. Keefer, *ibid.*, **86**, 687 (1964).

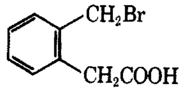
[4] B. Radyisiyewski and P. Wispek, *Ber.*, **18**, 1279 (1885).

were obtained using a Mel-Temp apparatus manufactured by Laboratory Devices, Cambridge, Mass. Essentially the same procedure was used in the stepwise conversion of *p*-xylene to *p*-methylbenzyl bromide (bp 215–220°), of the bromide to *p*-methylbenzyl cyanide [bp 100–105° (4 mm)], and of the nitrile to *p*-methylphenylacetic acid, mp 91–92° (lit.[5] mp 94°).

***o*-Bromomethylphenylacetic Acid.**—A mixture of 2.7 g of N-bromosuccinimide, 0.01 g of benzoyl peroxide, and 2.3 g of *o*-tolylacetic acid dissolved in a small volume of carbon tetrachloride was heated at reflux for a 2-hr period. The mixture was filtered and the filtrate was concentrated to dryness. The crystalline residue was recrystallized four times from carbon tetrachloride to provide 1.1 g (31% yield) of *o*-bromomethylphenylacetic acid, mp 129–132°.

Anal. Calcd for $C_9H_9BrO_2$ C, 47.18; H, 3.96; Br, 34.89. Found: C, 47.29; H, 4.14; Br, 34.70.

The position of the bromine atom was established through comparison of the nmr spectrum of this product with that of the parent *o*-tolylacetic acid. The spectrum of *o*-tolylacetic acid in deuteriochloroform (with tetramethylsilane (TMS) as the reference) has proton signals downfield at δ 2.28, 3.60, 7.11, and 11.43 which are assigned to CH_3, CH_2, ring H, and COOH, respectively, with the corresponding peak areas in the ratios 2.85, 2.13, 4.00, and 1.10. The spectrum of the monobromination product has proton signals at δ 3.88, 4.60, 7.32, and 9.83 with peak areas in the ratio 2.13, 1.85, 4.00, and 1.05, respectively. These are ascribed to CH_2 (bound to COOH), CH_2Br, ring H, and COOH in the following structure.



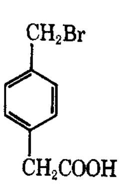
I

Further evidence of the preferential substitution of bromine at the methyl rather than the methylene carbon of *o*-tolylacetic acid is to be found in the fact that the spectrum of the halogenated material contains no peak in the methyl hydrogen region (δ 2–3). It is also pertinent that the peak ascribed to CH_2Br (δ 4.60) is near that (δ 4.30) for this group in the spectrum of *o*-methylbenzyl bromide.

***p*-Bromomethylphenylacetic Acid.**—A dilute solution of 7.3 g of *p*-tolylacetic acid in carbon tetrachloride was treated dropwise with 8.0 g of bromine in dilute solution in the same solvent.[1] The mixture was irradiated with a 750-w tungsten lamp during the addition. After the bromine was consumed the mixture was concentrated to dryness and the residue was recrystallized twice from toluene to provide 2.5 g (23% yield) of the bromo acid (II), mp 177–179°.

Anal. Calcd for $C_9H_9BrO_2$ C, 47.18; H, 3.96; Br, 34.89. Found: C, 46.89; H, 4.18; Br, 35.22.

A pure product was not obtainable when N-bromosuccinimide rather than bromine was used to brominate *p*-tolylacetic acid.



II

The position of the bromine atom in II was established through comparison of the nmr spectrum of the product and that of *p*-tolylacetic acid in hexadeuterioacetone (II was not appreciably soluble in deuteriochloroform). The carboxyl hydrogen signals for these two acids, as well as that for phenylacetic acid, are missing in the ketonic solvent. This is ascribed to H–D exchange with the medium. The spectrum of *p*-tolylacetic acid shows downfield peaks (TMS reference) at δ 2.28, 3.59, and 7.18 with area ratios of 3.22, 2.12, and 4.00, respectively, which are ascribed to CH_3, CH_2, and ring H. The brominated acid II showed no peak in the CH_3 region but had the characteristic ring H peaks (δ 7.39) and CH_2Br peaks (δ 4.64) with area ratios of 4.00:1.86. The carboxyl bound CH_2 peak (at δ 3.66) had an unaccountably large area (3.20 relative to 4.00 for the COOH peak). This peak may in fact incorporate a signal from a product of reaction of the parent bromo acid with impurities (water or diacetone alcohol) in the solvent.

Methyl *o*- and *p*-Tolylacetates.—These were prepared by esterification of the parent acids with diazomethane in ether solution. The liquid products were purified by distillation under reduced pressure.

The *ortho* isomer had bp 94–95° (3 mm), $n^{23}\mathrm{D}$ 1.5085.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.95; H, 7.27.

The *para* isomer had bp 92–94° (3 mm), $n^{23}\mathrm{D}$ 1.5030.

Anal. Found for $C_{10}H_{12}O_2$: C, 72.87; H, 7.25.

Methyl *o*- and *p*-Bromomethylphenylacetate.—Methyl *o*- and *p*-tolylacetates were brominated by the procedure used in brominating the parent *para* acid. The liquid product was purified by disillation at reduced pressure.

The *ortho* isomer had bp 154–156° (14 mm).

Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.40; H, 4.56; Br, 32.87. Found: C, 49.28; H, 4.46; Br, 33.10.

The *para* isomer had bp 123–128° (3 mm).

Anal. Found for $C_{10}H_{11}BrO_2$: C, 49.44; H, 4.53; Br, 32.92.

The nmr spectra of the bromo esters were compared with those of the parent esters (deuteriochloroform solvent, TMS reference). The spectrum of methyl *o*-methylphenylacetate shows proton signals at δ 7.17 (ring H), 3.67 ($COOCH_3$),[6] 4.63 (CH_2), and 2.30 (ring-substituted CH_3). The peak areas of the signals at δ 3.67 and 4.63 are in a 3:2 ratio. The spectrum of the bromination product of this ester is similar but it lacks the ring-substituted methyl signal in the δ 2.3 region and has a new signal at δ 4.62 (of area 1.70 relative to a peak area of 4 for ring H, δ 7.30) which is ascribed to CH_2Br. It is interesting that the methylene hydrogen (δ 3.83) and $COOCH_3$ hydrogen signals (δ 3.74) are in reverse positions in the unbrominated and brominated ester (the methyl ester of I).

The brominated *para* ester (the methyl ester of II) has a spectrum very similar to that of its *ortho* isomer with signals at δ 7.25 (ring H), 4.40 (CH_2Br), 3.62 ($COOCH_3$), and 3.55 (CH_2). The unbrominated *para* ester provides proton signals at δ 7.08 (ring H), 3.57 ($COOCH_3$), 3.49 (CH_2), and 2.24 (ring-substituted CH_3).

3-(*o*-Tolyl)propionic Acid.—*o*-Methylcinnamic acid was prepared as described previously[7] and reduced (in 72% yield) to the corresponding hydrocinnamic acid, 3-(*o*-tolyl)propionic acid by the procedure of Page and Tarbell,[8] mp 102–104° (lit.[9] mp 102°)

3-(*o*-Bromomethylphenyl)propionic Acid.—A 5.0-g (0.030 mole) sample of 3-(*o*-tolyl)propionic acid in carbon tetrachloride was photobrominated (using an equimolar quantity of bromine) by the procedure used in brominating *p*-tolylacetic acid. The crude product, after recrystallization from hexane weighed 5.0 g (68% yield), mp 91–100°. After several recrystallizations from a 1:2 mixture of benzene and ligroin the melting point was raised to 103–105°. The bromine content of this material was determined by hydrolysis of a weighed sample with refluxing NaOH solution followed by Volhard titration of the hydrolysate.

Anal. Calcd for $C_{10}H_{11}BrO_2$: Br, 32.9. Found, Br, 32.2.

The nmr spectrum of this product in 10% solution in deuteriochloroform is summarized in Table I. The identification of the various proton signals, as they are listed in this table, is based on an analysis of the nmr spectra of a number of structurally related compounds in $CDCl_3$. The δ 11.20 peak is assigned to COOH since in the model compounds the carboxyl proton signals are in every case at the lowest field strength of all proton signals. In 3-(*o*-tolyl)propionic acid, 3-phenylpropionic acid,[10] and 3-phenyl-3-bromopropionic acid[11] this peak appears at δ 11.2, 11.8, and 11.9, respectively. The peak at δ 7.30 is assigned to ring H and is generally present in this region in all of the disubstituted benzenes under consideration in this investigation. The peak at δ 5.64 is assigned to a CHBr group directly attached to the aromatic ring. The signal for this group appears somewhat further downfield from that of the same group in the spectrum of the model compound, 3-phenyl-3-bromopropionic acid. The

---

(5) P. Schorigin, *Ber.*, **43**, 1948 (1910).

(6) R. M. Silverstein and G. C. Bassler, "Spectrophotometric Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1964, p 84.

(7) Young, *Ber.*, **25**, 2102 (1892).

(8) G. A. Page and D. S. Tarbell, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 13.

(9) W. v. Miller and Rohde, *Ber.*, **23**, 1890 (1898).

(10) A. W. Ingersoll, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p 136.

(11) R. Fittig and F. Binder, *Ann.*, **195**, 131 (1879).

TABLE I

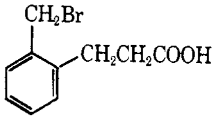
NMR SPECTRUM ($CDCl_3$ SOLVENT) OF THE BROMINATION PRODUCT OF 3-(o-TOLYL)PROPIONIC ACID

Proton signal[a] (δ, ppm)	Rel[b] peak areas	Signal source
11.20	0.93	COOH
7.30	4.00	ring H
5.64	0.80	CHBr
4.62	0.75	CH_2Br
3.40	1.75	CH_2
2.49	1.65	Ring CH_3

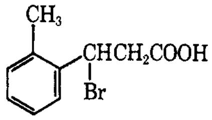
[a] Tetramethylsilane reference. [b] Relative to a value of 4.00 for the peak at δ 7.30.

δ 4.62 peak (ascribed to CH_2Br) also appears a bit downfield from that (δ 4.30) for the same group in the spectrum of *o*-methylbenzyl bromide. Actually the spectrum of brominated 3-(*o*-tolyl)propionic acid shows several peaks in the δ 2.7–3.6 region with a major peak at δ 3.40. These are all characterized as methylene peaks, and the major signal which also appears in the spectrum of 3-phenyl-3-bromopropionic acid is ascribed to a methylene immediately adjacent to a carboxyl group. The peak farthest upfield (δ 2.49), as in the case of compounds considered above, is ascribed to ring substituted CH_3.

The product of bromination of 3-(*o*-tolyl)propionic acid is, therefore, considered to be a mixture of III and IV.



III



IV

It is considered unlikely that bromination should have occurred to any significant extent at a nonbenzylic position. It is reasoned that the mixture is about two parts IV and one part III since the areas of the peaks corresponding to CHBr and CH_2Br are in a 1:1 ratio. This reasoning is upheld by the fact that, if the product were all IV, the peak areas at δ 2.49 (CH_3) and δ 7.30 (ring H) should be in the ratio 3:4 while the observed ratio is of the order of 2:4; that is, only two-thirds of the molecules of the isomeric product mixtures contain ring-bound methyl groups.

1- and 4-Fluorenecarboxylic Acids.—The 1 isomer was obtained from K and K Laboratories, Inc. The 4 isomer was prepared by cyclization[12] of diphenic acid to 4-carboxyfluoren-9-one followed by Wolff–Kishner reduction of the latter;[13] melting point of the acidic product was 194–194.5° (lit.[13] mp 191–192°).

9-Bromofluorene-1- and -4-carboxylic Acids.—A sample of 9-bromofluorene-1-carboxylic acid was prepared by a procedure described previously.[2] 4-Fluorenecarboxylic acid (8.7 g) was treated with 7.2 g of bromine, and the crude product was isolated by essentially the same procedure as described above for bromination of *p*-tolylacetic acid. The crude 9-bromofluorene-4-carboxylic acid was recrystallized from acetic acid, yield 6.5 g (54%), mp 198–204° dec. This material, which contained only 79.2% of the theoretical quantity of bromine, was used in the rate studies. No bromination procedure was discovered which provided an analytically pure sample of this bromo acid.

1- and 4-Fluoreneacetic Acids.—4-Fluorenecarboxylic acid was converted to 4-fluoreneacetic acid by the method of Bachmann and Sheehan.[14] In preparing 1-fluoreneacetic acid a 10-g sample of 1-fluorenecarboxylic acid was converted to its acid chloride by 60-min reflux with 10 ml of thionyl chloride. The excess thionyl chloride was removed under reduced pressure, and the residue was dissolved in a mixture of 50 ml of dioxane and 100 ml of absolute ether. A solution of 5.6 g of diazomethane in ether was added dropwise with stirring to the acid chloride solution, the temperature of which was maintained at 0° during the addition. The solvent was removed under reduced pressure and the crude diazo ketone was dissolved in 70 ml of dioxane. This solution was added dropwise over a 1-hr period to a stirred suspension of 8.2 g of silver oxide in a solution of 21.4 g of sodium thiosulfate in 435 ml of water. The temperature of the suspension was maintained at 60° during the addition. The resultant mixture was stirred 1 hr longer, then treated with decolorizing carbon, cooled, and filtered. The filtrate was acidified with dilute acetic acid. The precipitated 1-fluoreneacetic acid (4.6 g, 43% yield) was crystallized from benzene, mp 180–183°.

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.33; H, 5.40. Found: C, 80.11; H, 5.30.

9-Bromofluorene-1-acetic Acid and 9-Bromofluorene-4-acetic Acid.—Samples (2 g) of 1- and 4-fluoreneacetic acids were brominated by much the same method that was used in brominating *p*-tolylacetic acid. The crude products were crystallized from nitromethane. Both of the bromides are unstable at relatively low temperatures, and products of high purity were not obtained. The 9-bromofluorene-1-acetic acid was obtained in 1.1-g yield, mp 190–195° dec.

Anal. Calcd for $C_{15}H_{11}BrO_2$: Br, 26.4. Found: Br, 26.7.

The 9-bromofluorene-4-acetic acid was obtained in 2.0-g yield, mp 210–214° dec.

Anal. Found for $C_{15}H_{11}BrO_2$: Br, 27.5.

The location of the bromine atom at the 9 position is based on the results of two comparative rate studies. In the first of these 1 equiv each of phenylacetic acid and of toluene in solution in dry benzene were photobrominated with 1 equiv of bromine. The product solution was extracted with dilute sodium hydroxide solution. The aqueous extract was found to contain only 20% of the theoretical quantity of bromine. The bromination rates of toluene and phenylacetic acid are, therefore, in the ratio of 4:1. In a similar experiment equivalent amounts of fluorene and toluene were allowed to compete for 1 equiv of bromine. Analysis of the product solution by vapor phase chromatography indicated that essentially all of the toluene initially present remained in unreacted form. It follows that the 9 position of the fluorene molecule must be much more reactive than the methylene of a CH_2COOH substituent at another position in the molecule.

Kinetic Experiments.—The methods used in purifying dioxane and in investigating the rates of hydrolysis of the various bromo acids and bromo esters in aqueous dioxane were essentially the same as those employed in previous investigations.[1,3a]

In most runs 80% dioxane, prepared by mixing 20 volumes of water and 80 volumes of dioxane at room temperature, was used as the solvent. A few runs on the carboxybenzyl bromides were made in which the organic reactant was present in the form of its conjugate base rather than the free acid. These runs were initiated by mixing equal volumes of 80% aqueous dioxane solutions of sodium hydroxide and the bromo acid. The concentrations of the base and the acid in these solutions were the same.

In those runs in which the starting bromides were not analytically pure, notably those in which 9-bromofluorene-4-carboxylic acid was used, the initial concentrations of the organic halides were assigned on the basis of bromide ion concentrations of the reaction mixtures as measured at infinite reaction times.

The Products of Hydrolysis of *o*-Carboxybenzyl Bromide and *o*-Bromomethylphenylacetic Acid.—Samples of the two bromo acids were hydrolyzed in 80% aqueous dioxane at 87.4°. Each reaction was allowed to proceed for at least 8 half-lives. The solvent was then removed and the residue was crystallized from water. The product isolated from the *o*-carboxybenzyl bromide was phthalide, mp 74–75°.

Anal. Calcd for $C_8H_6O_2$: equiv wt, 134.6. Found: equiv wt, 133.7.

The material obtained from *o*-bromomethylphenylacetic acid was the lactone of *o*-hydroxymethylphenylacetic acid, mp 84–84.5°.

Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.83; H, 5.26.

These same two products were isolated when the hydrolyses were conducted with sodium hydroxide initially present in the reaction mixture at the same concentration as the bromo acid.

Results

Solvolysis rate constants, k_s (3), for the various benzyl and fluorenyl bromides under investigation are reported in Table II.

$$\ln([RBr]_i/[RBr]_t) = k_s t \qquad (3)$$

Reported constants were calculated from the slopes of the lines obtained by plotting experimental values of

---

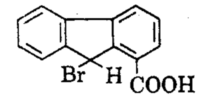
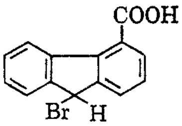
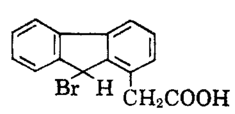
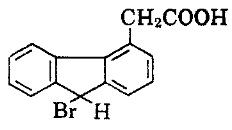
[12] F. Bischoff and H. Adkins, *J. Am. Chem. Soc.*, **45**, 1030 (1923).

[13] E. Weisburger and J. Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).

[14] W. E. Bachmann and J. C. Sheehan, *ibid.*, **62**, 2687 (1940).

TABLE II

RATE CONSTANTS FOR HYDROLYSIS OF THE BROMIDES

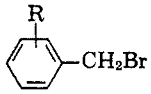
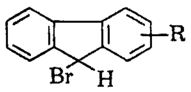
Range of $[RBr]_i$, mole/l.	Solvent	Temp, °C	$10^5 k_s$, sec^{-1}
	o-$BrCH_2C_6H_4COOH$		
0.061–0.079	80% aq dioxane	87.4	210.3 ± 0.3
0.094–0.13[a]	80% aq dioxane	87.4	211.9 ± 3.8
0.068–0.088[b]	80% aq dioxane	87.4	196.6 ± 1.2
. . .	80% aq dioxane	87.7	231 ± 13[c]
0.056–0.086	50% aq dioxane	70.1	323.3 ± 3.4
0.050–0.064[a]	50% aq dioxane	70.1	251 ± 12
0.056–0.069[b]	50% aq dioxane	70.1	227 ± 15
0.074–0.087[d]	50% aq dioxane	70.1	338.9 ± 7.9
	p-$BrCH_2C_6H_4COOH$		
0.032–0.053	50% aq dioxane	70.1	7.92 ± 0.04
0.050–0.057[a]	50% aq dioxane	70.1	6.27 ± 0.32
0.040–0.053[b]	50% aq dioxane	70.1	6.02 ± 0.40
0.042–0.054[d]	50% aq dioxane	70.1	6.59 ± 0.37
0.0314[e]	80% aq dioxane	70.1	8.63
0.0380[e]	80% aq dioxane	70.1	8.82
. . .	80% aq dioxane	71.4	0.78 ± 0.02[c]
	o-$CH_3C_6H_4CH_2Br$		
0.085–0.236	80% aq dioxane	70.1	5.39 ± 0.02
	p-$CH_3C_6H_4CH_2Br$		
0.131–0.189	80% aq dioxane	70.1	5.73 ± 0.15
	o-$BrCH_2C_6H_4CH_2COOH$		
0.048	50% aq dioxane	24.5	0.91
0.022–0.040	70% aq dioxane	70.1	13.34 ± 0.34
0.020[f]	70% aq dioxane	70.1	14.81
0.012–0.019	70% aq dioxane	87.4	52.6 ± 0.8
	p-$BrCH_2C_6H_4CH_2COOH$		
0.019–0.049	70% aq dioxane	70.1	8.28 ± 0.0
0.025–0.026[g]	70% aq dioxane	70.1	235 ± 14
0.012–0.024	70% aq dioxane	87.4	35.2 ± 1.8
	o-$BrCH_2C_6H_4CH_2COOCH_3$		
0.029–0.056	70% aq dioxane	70.1	3.47 ± 0.11
0.049–0.078	70% aq dioxane	87.4	13.4 ± 1.2
	p-$BrCH_2C_6H_4CH_2COOCH_3$		
0.039–0.071	70% aq dioxane	70.1	4.51 ± 0.06
0.032–0.052	70% aq dioxane	87.4	17.7 ± 0.5
	$C_6H_5CH(Br)CH_2COOH$		
0.048–0.099	80% aq dioxane	70.1	3.79 ± 0.17
			
0.044–0.088	80% aq dioxane	70.1	0.269 ± 0.023
0.025–0.053	70% aq dioxane	70.1	0.776 ± 0.029
0.013–0.034[h]	70% aq dioxane	70.1	149.2 ± 0.4
0.023–0.035	80% aq dioxane	87.4	1.28 ± 0.04
			
0.041–0.082	80% aq dioxane	70.1	1.20 ± 0.05
0.020–0.034	70% aq dioxane	70.1	2.17 ± 0.10
0.018–0.032[h]	70% aq dioxane	70.1	215.9 ± 2.7
0.023–0.031	80% aq dioxane	87.4	6.33 ± 0.20
			
0.043[i]	80% aq dioxane	70.1	81
			
0.049[j]	80% aq dioxane	70.1	87

[a] $[HBr]_i = 0.05\ M$. [b] $[HBr]_i = 0.20$ M. [c] From ref 1. [d] $[NaBr]_i = 0.20\ M$. [e] $[NaOH]_i = [RBr]_i$. [f] $[HBr]_i = 0.084\ M$. [g] $[NaOH]_i = 0.030\ M$. [h] $[NaOH]_i = 0.080\ M$; plots of log [RBr] *vs.* time are linear to better than 60% of completion of the reactions; there is no evidence of rate dependence on $[OH^-]$. [i] Purity of the starting organic bromide is 98% as based on an analysis for halogen. [j] Purity of the starting organic bromide is 96% as based on an analysis for halogen.

log $[RBr]_t$ *vs.* time, *t*. In most instances these lines remained straight to high percentages of completion of reaction. Reactivity ratios of certain of the *ortho*- and *para*-substituted benzyl bromides and of the 1- and 4-substituted fluorenyl bromides under investigation are summarized in Table III.

TABLE III

SOLVOLYSIS RATE CONSTANT RATIOS FOR THE ISOMERIC SUBSTITUTED BENZYL AND FLUORENYL BROMIDES (70.1°)

Solvent	R	$10^5 k_s$, sec^{-1}	$k_s(ortho)/k_s(para)$
			
80% aq dioxane	o-CH_3	5.4	0.9
80% aq dioxane	p-CH_3	5.7	
70% aq dioxane	o-CH_2COOH	13.3	1.6
70% aq dioxane	p-CH_2COOH	8.3	
70% aq dioxane	o-CH_2COOCH_3	3.5	0.8
70% aq dioxane	p-CH_2COOCH_3	4.5	
80% aq dioxane	o-COOH	68.1	87[a]
80% aq dioxane	p-COOH	0.78	
			
			$k_s(1-R)/k_s(4-R)$
80% aq dioxane	1-COOH	0.3	0.2
80% aq dioxane	4-COOH	1.2	
80% aq dioxane	1-CH_2COOH	81	0.9
80% aq dioxane	4-CH_2COOH	87	

[a] At 71.4°; from ref 1.

Reactions of the *o*- and *p*-Carboxybenzyl Bromides.— The majority of the rate runs on these two bromides were conducted at 70.1° with 50% aqueous dioxane as the solvent. Under these conditions the ratio of k_s values for *ortho*:*para* isomers is of the order of 40:1, approximately one-half that reported previously[1] (see Table III) for reaction in 80% aqueous dioxane at a comparable temperature. A check value of k_s for reaction of the *ortho* isomer in 80% aqueous dioxane, which was obtained in this investigation, is in good agreement with that obtained earlier. The drop in the intensity of the *o*-carboxyl group effect on reactivity with increasing water content of the medium may be a reflection of a corresponding increase in the capacity of the medium itself to promote polarization of the carbon–bromine bond at the reaction center. Alternately this drop might be ascribed to a deactivation of *o*-COOH as a participating group as water replaces dioxane in its surrounding cage of solvent molecules.

In both 80 and 50% aqueous dioxane k_s values for the *ortho* isomer fall only slightly when hydrogen bromide is initially present in the reaction mixture, and added hydrogen bromide has effects of similar magnitude on k_s values for hydrolysis of *p*-carboxybenzyl bromide. It is highly unlikely, therefore, that the high reactivity of the *ortho* isomer is to be ascribed to the functioning of the anion, *o*-$BrCH_2C_6H_4COO^-$, as a reaction intermediate as depicted in eq 1. Dissociation of the weak parent acid should be subject to strong repression by added hydrogen bromide. If, therefore, any significant fraction of the reaction of *o*-carboxybenzyl bromide occurred by a process in which the anion served as a precursor of the final product, a high sensitivity of k_s to hydrogen bromide content of the medium should have been observed.

It is interesting to report, however, that evidence has been obtained that the *o*-COO^- group is indeed functionally capable of participation in the solvolysis of the anion (*o*-$BrCH_2C_6H_4COO^-$) itself. Some runs were made both with *o*- and *p*-carboxybenzyl bromide in which sodium hydroxide was initially present in the medium in concentration equal to that of the starting acid. Under these conditions the starting bromo acids were actually in the form of their salts rather than of the free acids. As can be explained on inductive grounds, the bromo acid hydrolyzes appreciably more readily in its salt form than in the form of the free acid (*cf.* k_s values for the runs on the salts in 80% aqueous dioxane with those at the same temperature, 70.1°, on the free acids in 50% aqueous dioxane). In the case of the salt of the *o*-bromo acid, hydrolysis at 70.1° in 80% aqueous dioxane was found to occur so rapidly that rate measurements could not be made. It was observed that the reaction was essentially complete in 165 sec. Assuming that at least 8 half-lives had elapsed by this time, it can be calculated that the reaction has a minimum k_s value of 0.03 sec^{-1}. The reactivity ratio for the *ortho*:*para* isomers of $BrCH_2C_6H_4COO^-$ is of the order of 300 or more. It seems likely that this high ratio is to a considerable degree a reflection of the capacity of *o*-COO^- to function as an internal nucleophile in promoting the hydrolysis reaction.

The possibility that the reactions of the anions (*o*- and *p*-$BrCH_2C_6H_4COO^-$) might have resulted in the formation of ester linkages (eq 4) can be discounted.

$$2BrCH_2C_6H_4COO^- \longrightarrow BrCH_2C_6H_4COOCH_2C_6H_4COO^- \quad (4)$$

The product of the reaction of the *ortho* isomer is phthalide rather than an ester (see Experimental Section). The reaction of the *para* isomer obeys a first-order rate law (eq 3) to high percentages of completion, which would not be the case for an ester-producing process.

Reactions of *o*- and *p*-Bromomethylphenylacetic Acids and Their Methyl Esters.—At 70.1° the k_s value for the hydrolysis of *o*-bromomethylphenylacetic acid in 70% aqueous dioxane is 1.6 times that for its *para* isomer. In circumstances such that the substituents are functionally incapable of nucleophilic participation, the rate constant ratios for solvolysis of *ortho*- and *para*-substituted benzyl bromides are generally somewhat (but not much) less than unity (see Table III).[15] There is, therefore, no convincing argument for COOH participation in the solvolysis of an *ortho*-substituted benzyl bromide when the carboxyl group in the *ortho* substituent is separated from the aromatic ring by a methylene group. The corresponding *ortho*:*para* reactivity ratio for the methyl esters of these bromo acids (70.1°, 70% aqueous dioxane) is about 0.8. Thus the evidence for participation of the *ortho* substituent ($COOCH_3$) in the hydrolysis of methyl *o*-bromomethylphenylacetate is also negative.

The lack of *ortho*-substituent participation in the reaction of *o*-bromomethylphenylacetic acid is tentatively explained on geometric grounds. The close approach of the COOH group and the departing bromine required for effective hydrogen bonding (O–H–Br) in the transition state of the solvolysis process may well be subject to an energetically unfavorable H–H interaction involving the two side chain methylene groups. In explaining the fact that the $COOCH_3$ group does not participate effectively in the hydrolysis of *o*-carbomethoxybenzyl bromide (see the introduction), it has been suggested[1] that in the transition state the methylene group from which the bromine is departing must assume a coplanar arrangement with the aromatic ring. Apparently the conformational barrier to carbomethoxy participation which is created by this arrangement is not reduced when the carbomethoxy group is contained in the side chain, *o*-CH_2COOCH_3, rather than attached directly to the ring.

There is evidence that the *o*-CH_2COO^- group may participate in the hydrolysis of *o*-$BrCH_2C_6H_4CH_2COO^-$, although it is not perhaps as convincing as the corresponding evidence relating to the reaction of *o*-$BrCH_2C_6H_4COO^-$. The sodium salt of *o*-bromomethylphenylacetic acid is essentially completely hydrolyzed in 1.25 sec at 70.1° in 70% aqueous dioxane. Assuming that at least 8 half-lives elapse during this period, a *minimum* value of k_s = 0.04 sec^{-1} can be calculated for the reaction. The structural features which prevent the close approach of COOH and Br in the transition state for the reaction of the free acid do not forestall the close approach of the COO^- group and the carbon at the reaction center which is required for nucleophilic displacement of departing bromide ion. The k_s value for the *para* isomer of this salt is about one-fifteenth this figure (see Table II). As in the case of *p*-carboxybenzyl bromide, the salt of *p*-bromomethylphenylacetic acid is substantially more reactive than the free acid; the free acid, however, does not hydrolyze by a process in which *p*-$BrCH_2C_6H_4CH_2COO^-$ is an intermediate, since the rate of the reaction is not markedly affected by the addition of hydrogen bromide to the medium.

The Reaction of 3-(*o*-Bromomethyl)phenylpropionic Acid.—On the basis of an examination of a molecular model, it seemed worthwhile to consider the possibility that the carboxyl group of this bromo acid might provide for internal electrophilic catalysis when hydrolysis takes place. It is now considered unlikely that such participation occurs extensively in view of the results obtained in studying the hydrolysis of the product of bromination of 3-(*o*-tolyl)propionic acid. This material, as used in kinetic work (see Experimental Section), was approximately one-third 3-(*o*-bromomethyl)-phenylpropionic acid (III) and two-thirds the isomeric 3-bromo-3-(*o*-tolyl)propionic acid (IV). As shown in Figure 1, one of the components of this mixture was appreciably more reactive than the other. The slope of a plot of log [RBr] *vs.* time for reaction of the mixture of the two bromides in 80% aqueous dioxane falls off rapidly in early phases of the reaction and then levels off to a relatively constant value. It is assumed that in the later phase of the reaction, when the slope no

---

[15] See also G. M. Bennett and B. Jones, *J. Chem. Soc.*, **1815** (1935), and other references cited previously.[1]

longer changes, the more reactive of the two bromides has already been totally hydrolyzed. The rate constant for the less reactive isomer is calculated from the straight portion of line A (toward the end of reaction) as $k_s = 1.6 \times 10^{-5}$ sec^{-1} (70.1°). By extrapolating this straight section of A to initial reaction time, it has been established that the slower reacting of the two isomers constitutes over 60% of the starting bromide. It is, therefore, presumed to be IV. One would expect this compound to hydrolyze at a rate comparable with that for 3-bromo-3-phenylpropionic acid [$C_6H_5CH(Br)$-CH_2COOH] and, in fact, the k_s value obtained for the the latter acid (Table II) is about twice that which is approximated for IV. The initial concentration of 3-(*o*-bromomethyl)phenylpropionic acid (III), established through estimation of the initial concentration of IV, has been used as $[RBr]_i$, eq 3, in analyzing the data for the early phases of the reaction. That is, it has been assumed that at the outset, essentially all of the bromide which is consumed is the more reactive of the two isomers (presumably III) and the k_s value for this compound has been calculated from the slope of the plot of [III] *vs.* time near the start of reaction (line B, Figure 1). The k_s value thus obtained (37×10^{-5} sec^{-1}) is six to seven times as large as those obtained for *o*- and *p*-methylbenzyl bromides (Table II) under comparable reaction conditions. While it is a bit surprising that III is much more reactive than structurally related compounds in which there is no chance of *ortho*-substituent participation, the magnitude of the reactivity difference is not great enough to suggest extensive carboxyl group involvement in the reaction of III. Even if the structural identification of the slow- and fast-reacting bromo acids were reversed, a comparison of k_s values with those for the methylbenzyl bromides would not support an argument for such involvement.

Reactions of 9-Bromofluorene-1- and -4-carboxylic Acids and 9-Bromofluorene-1- and -4-acetic Acids.—It has been shown previously[2] that the carbomethoxy group does not participate in the hydrolysis of the methyl ester of 9-bromofluorene-1-carboxylic acid, and this is ascribed to an unfavorable geometric situation which is related to the structural rigidity of the ring system. Neither does the carboxyl group participate in the hydrolysis of the bromo acid itself. Actually this compound reacts at a rate substantially less than that for the isomeric 9-bromofluorene-4-carboxylic acid (Table III). It is reasoned, on the basis of an examination of a molecular model of 9-bromofluorene-1-carboxylic acid, that the molecule is sufficiently inflexible so that significant interaction between the bromine and carboxyl hydrogen cannot take place. When the carboxyl is separated one carbon from the ring, this geometric situation is somewhat improved. The improvement is not, however, sufficient to lead to carboxyl participation in the hydrolysis of 9-bromofluorene-1-acetic acid. This compound is, in fact, slightly less reactive than the isomeric 9-bromofluorene-4-acetic acid under the conditions employed (Table III).

The sodium salts of 9-bromofluorene-1- and -4-carboxylic acid hydrolyze much more rapidly than the free acids, but the two salts are of comparable reactivity (Table II). Contrary to what is observed in the reactions of o-$BrCH_2C_6H_4COO^-$ and o-$BrCH_2C_6H_4CH_2COO^-$, the COO^- group does not participate appreciably in the reaction of 9-bromofluorene-1-carboxylate ion. Rather the high reactivity of this ion as compared to that of the free acid must be explained entirely on inductive grounds.

It is interesting to consider the possibility that the high reactivity of *o*-carboxybenzyl bromide is not the result of a molecular geometry uniquely favorable for electrophilic catalysis of reaction by the carboxyl group but rather that it relates to the capacity of this substituent to cage itself with water molecules. This aggregation of solvent in the near vicinity of the reaction center might facilitate the activation process.

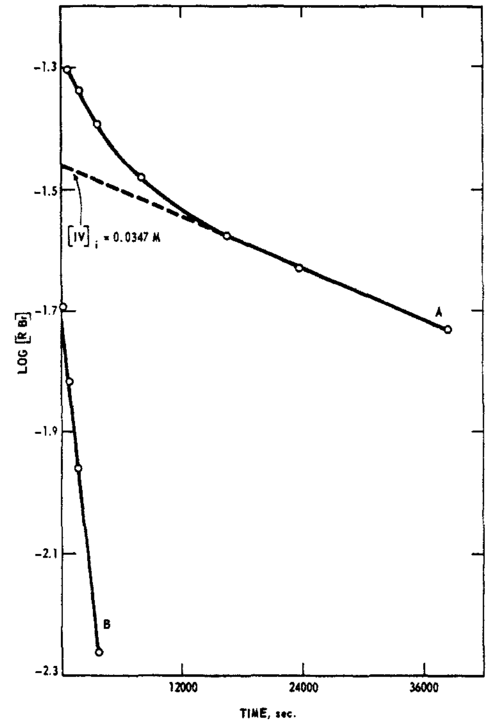
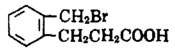
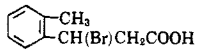


Figure 1.—The hydrolysis of monobrominated 3-(*o*-methylphenyl)propionic acid in 80% aqueous dioxane at 70.1°. The starting bromide is assumed to be a mixture of III and IV below.



III



IV

The points for curve A are based on the total organic bromide concentration [III and IV] with $[RBr]_i = 0.0551$ *M*. Curve B is based on the concentration of III only with $[RBr]_i = 0.0204$ *M*.

Table IV

Energies and Entropies of Activation for Hydrolysis of Substituted Benzyl and Fluorenyl Bromides

Compound	Solvent	*E*, kcal[a]/mole	ΔS*, eu
9-Bromofluorene-1-carboxylic acid	80% aq dioxane	22.2 ± 1.3	−21.8 ± 3.8
9-Bromofluorene-4-carboxylic acid	80% aq dioxane	23.6 ± 0.8	−14.7 ± 2.3
o-Bromomethylphenylacetic acid	70% aq dioxane	19.5 ± 0.4	−22.2 ± 1.1
p-Bromomethylphenylacetic acid	70% aq dioxane	20.6 ± 1.0	−19.5 ± 2.9
Methyl *o*-bromomethylphenylacetate	70% aq dioxane	19.3 ± 1.4	−25.1 ± 4.1
Methyl *p*-bromomethylphenylacetate	70% aq dioxane	19.4 ± 0.4	−24.5 ± 1.1

This explanation seems unlikely, however, since it should extend to the hydrolysis of 9-bromofluorene-1-carboxylic acid; yet this reaction is not subject to any unusual carboxyl group effect.

Thermodynamic Constants.—The energies and entropies of activation for those hydrolyses which were investigated at two temperatures (Table II) are recorded in Table IV. As would be expected (since the evidence for *ortho*-substituent or 1-substituent participations is negative for those reactions covered by the table), the energies of activation for the two members of each pair of isomers are similar in value.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

The Hydrolysis of Carboxylic Anhydrides. VII.[1,2] Electrolyte Effects on the Acid Hydrolysis

C. A. BUNTON AND J. H. FENDLER

The Department of Chemistry, University of California, Santa Barbara, California, and William Ramsay and Ralph Forster Laboratories University College, London, England

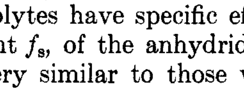
Received May 24, 1966

Aqueous perchloric, sulfuric, and hydrochloric acids catalyze hydrolyses of trimethylacetic and camphoric anhydrides to different extents, but their specificities depend largely upon their electrolyte effects upon the activity coefficients of the anhydrides. The variation of rate of hydrolysis of benzoic anhydride in water with acidity is very complex, but if the ionic strength is maintained with added electrolyte the rate increases smoothly with increasing concentration of perchloric or hydrochloric acid. Provided that allowance is made for variations in the activity coefficients of camphoric and trimethylacetic anhydrides the rates of their acid hydrolyses are dependent in a simple way upon the protonating power of the acid and the water activity. Some studies were made of salt effects upon the spontaneous hydrolyses, and the deuterium isotope effect upon it.

The hydrolyses of carboxylic anhydrides in aqueous acids generally follow A2 mechanisms,[3-5] although the acid hydrolysis of acetic mesitoic anhydride follows an A1 mechanism[4] because of the stability of the mesitoyl cation.[6]

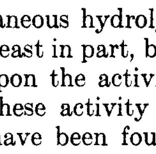
For acid hydrolyses of many substrates the rate constants are approximately proportional either to the acid concentration, or to its protonating power as measured by Hammett's acidity function, and mechanistic criteria have been based on these rate relations.[7] Bunnett has suggested a modification of these criteria in which the reaction rate is related to both acidity and water activity.[8] However, for the hydrolyses of acetic and trimethylacetic anhydrides in aqueous acid, there is no simple relationship between reaction rate and acidity, even when changes in the water activity are taken into account, and the catalytic powers of the acids differ considerably.[5] Sulfuric acid is a more effective catalyst than either perchloric or hydrochloric acids. These observations suggest that the strong acids are affecting the reaction rate by acting both as proton donors and as electrolytes, and their electrolyte effects could well be specific. Specific electrolyte effects have been observed for many hydrolyses both of uncharged and protonated carboxylic acid derivatives, and of some esters of inorganic acids.[9-11]

The salt effects upon the spontaneous hydrolysis of acetic anhydride in water arise, at least in part, because electrolytes have specific effects upon the activity coefficient f_s, of the anhydride.[11] These activity effects are very similar to those which have been found for other carbonyl compounds,[12,13] in that anions of low charge density, *e.g.*, perchlorate, decrease f_s, whereas anions of high charge density, *e.g.*, sulfate, increase it. If acids, acting as electrolytes, have specific differential effects upon the activity coefficients of the initial and transition states of hydrolysis, they should also have different catalytic efficiencies. We have therefore measured the activity coefficients of some carboxylic anhydrides in aqueous acids, and attempted to relate them to the reaction rates in the acids. In order to make meaningful comparisons we chose anhydrides for which the rate of the spontaneous hydrolysis is much less than that of the acid hydrolysis, because an acid, acting as an electrolyte, should affect the rate of the spontaneous hydrolysis. Acetic anhydride is rapidly hydrolyzed in aqueous acid,[5,14] and therefore less reactive anhydrides had to be studied. Trimethylacetic (I), camphoric (II), and benzoic anhydrides are all



$(CH_3)_3C\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}C(CH_3)_3$

I



II

---

[1] Part VI: C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *J. Chem. Soc.*, 6174 (1965).

[2] This work was supported in part by Grant G.P. 2889 from the National Science Foundation. This support is gratefully acknowledged.

[3] J. Koskikallio, D. Pouli, and E. Whalley, *Can. J. Chem.*, **37**, 1360 (1959).

[4] C. A. Bunton and S. G. Perry, *J. Chem. Soc.*, 3070 (1960).

[5] C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, **30**, 1365 (1965).

[6] M. S. Newman in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 4.

[7] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957); F. A. Long and M. A. Paul, *ibid.*, **57**, 935 (1957).

[8] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961).

[9] S. Marburg and W. P. Jencks, *ibid.*, **84**, 232 (1962); E. S. Hand and W. P. Jencks, *ibid.*, **84**, 3595 (1962); T. H. Fife, *ibid.*, **87**, 4597 (1965); J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2009 (1957).

[10] C. A. Bunton and T. Hadwick, *ibid.*, 3248 (1958); 943 (1961); J. G. Tillett, *ibid.*, 5138 (1960); P. W. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhala, B. Silver, C. A. Vernon, and V. A. Welch, *ibid.*, 227 (1966); C. A. Bunton and G. Schwerin, *J. Org. Chem.*, **31**, 842 (1966).

[11] C. A. Bunton, N. A. Fuller, S. G. Perry, and I. Pitman, *J. Chem. Soc.*, 4478 (1962).

[12] F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).

[13] A. P. Altshuller and H. E. Everson, *J. Am. Chem. Soc.*, **75**, 4823 (1953); G. M. Waind, *J. Chem. Soc.*, 2879 (1954).

[14] V. Gold and J. Hilton, *ibid.*, 838, 843 (1955).