Neighboring Ortho Carboxyl Group Participation and α-Deuterium Isotope Effects in the Hydrolysis of Benzyl Bromides

V. P. Vitullo,* S. Sridharan, and L. P. Johnson[1]

Contribution from the Laboratory for Chemical Dynamics, Department of Chemistry, University of Maryland Baltimore County, Catonsville, Maryland 21228.

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Abstract: The pH-rate profile for the hydrolysis of *o*-carboxybenzyl bromide (HA) in 50% aqueous dioxane solution (μ = 0.50 M, $NaClO_4$) has been determined. In addition, α-deuterium isotope effects on this hydrolysis have been determined in the pH range of 0.56-4.52. Although the anion (A^-) is some 15 000 times as reactive as the acid (HA), the α-D effect per D is 1.04 for hydrolysis of both forms of the substrate. Relative reactivities of benzyl, *o*-, and *p*-carboxybenzyl bromides in 50% aqueous dioxane (50D) are 1, 3.8, and 0.3, respectively. Results of these kinetic studies coupled with the experimental observation that no oxygen-18 is incorporated in phthalide, the sole product of hydrolysis of *o*-carboxybenzyl bromide, at both low (~0.56) and high (~4.4) pHs are taken as compelling evidence that the hydrolysis proceeds by intramolecular displacement of bromide by either *o*-COOH or *o*-COO^-.

Participation by a neighboring carbonyl group in reactions of certain alkyl and aralkyl halides is well documented.[2] A kinetic study[3] of the hydrolysis of carboxy substituted benzyl bromides has suggested that *o*-carboxybenzyl bromide (HA) reacts by an S_N1 route, the sole product being phthalide, whereas the para isomer reacts mainly by an S_N2 process. The enhanced reactivity of the *o*-carboxy substrate (HA) was rationalized in terms of electrophilic catalysis by the *o*-COOH group.

Shiner and Sieb[4] have demonstrated the usefulness of α-D isotope effects in deducing transition-state structures in the solvolysis of neophyl esters, which involves neighboring phenyl group participation. As part of our continuing study of α-deuterium isotope effects in solvolytic reactions,[5] we decided to investigate the influence of both protonated and ionized *o*-carboxyl groups on the α-D isotope effects in the hydrolysis of benzyl bromides.

Results and Discussion

Our pilot kinetic experiments on the hydrolysis of HA revealed certain discrepancies with the published data.[3] Attempts to reproduce the reported rate data for unbuffered solutions of 50 and 80% aqueous dioxane either spectrophotometrically or titrimetrically (pH-stat method) failed. Apparently, the high concentration of HA required in ref 3 for the conventional titrimetic procedure almost completely suppressed the dissociation of HA to A^-. For this reason, addition of even 0.20 M HBr (see ref 3b) failed to reduce the rate substantially. In addition, $k_{o\text{-COOH}}/k_{p\text{-COOH}}$ of 84-87 reported in ref 3 is in error because $k_{o\text{-COOH}}$ is in error.

Secondly, use of NaCl to maintain constant ionic strength also complicates the kinetics[6] because of nucleophilic reactions of chloride with the substrate. For example, at low pH (0.20 M H^+) for the hydrolysis of HA in 50D $k_{obsd} = 7.28 \times 10^{-5}$ s^{-1} (μ = 0.50 M, NaCl) and $k_{obsd} = 3.38 \times 10^{-5}$ s^{-1} (μ = 0.50 M, $NaClO_4$). Also, departures from first-order kinetics were noted in NaCl solutions after 3-4 half-lives. Results using NaCl as "inert electrolyte" in ref 3c should be interpreted with caution.

Thirdly, results using KNO_3 for salt-effect studies in ref 3c should be considered doubtful as NO_3^- has been shown to participate in displacement reactions of *p*-methoxybenzyl chloride in aqueous acetone solutions (see ref 7a).

The results of our kinetic studies of the hydrolysis of HA in 50D at 25 °C are shown in Table I. In all kinetic runs ionic strength of solutions was maintained at 0.50 M with $NaClO_4$ as inert electrolyte. The reaction does indeed show a pH dependence, the rate of hydrolysis increasing with pH.

Assuming that reaction takes place through both the acid (HA) and the anion (A^-) eq 1 may be derived

$$k_{obsd} = k_{HA} + (k_A\text{-}K_{HA})/(H^+) \qquad (1)$$

where k_{HA} and k_{A-} are rate constants for the hydrolysis of the acid and anion, respectively. The pH-rate profile shown in Figure 1 is based on the parameters obtained from a weighted least-squares analysis of k_{obsd} vs. $1/[H^+]$. As predicted, the relative contribution by A^- to the overall rate increases with pH. Using a pK_a value of 5.27 (see Experimental Section) for the equilibrium $HA \rightleftharpoons A^- + H^+$ in 50D (μ = 0.50 M $NaClO_4$), we estimate that at pH 4.52 the substrate is present to the extent of 15% as A^-. However, at this pH, >99.9% reaction proceeds through A^-. This is due to the fact that *o*-COO^- is some 15 000 times more reactive than the un-ionized form of the substrate.

Data for the relative reactivities of some relevant comparison substrates are shown in Table II. Benzyl bromide hydrolyzes slower than HA by a factor of 3.8. The ratio ($k_{o\text{-COOH}}/k_{p\text{-COOH}}$) is ca. 17, a result which reverses the usual trend of reactivities of ortho- and para-substituted substrates (see ref 2). These results strongly suggest that *o*-COO^- and *o*-COOH are both effective neighboring groups and that *o*-COO^- is significantly more effective than *o*-COOH.

Experiments in ^{18}O-enriched 50D (μ = 0.50 M, $NaClO_4$) at 25 °C provide compelling evidence that the *o*-COOH group does indeed participate in the displacement of bromide in the hydrolysis of *o*-carboxybenzyl bromide. Both at pH 0.56 and at pH 4.4 no oxygen-18 is incorporated in the product phthalide. This result precludes any mechanism which calls for nucleophilic interaction of H_2O with the benzylic carbon, and thereby rules out *o*-carboxybenzyl alcohol as an intermediate.

The data in Table I support the conclusion that both *o*-COOH and *o*-COO^- act as intramolecular nucleophiles in the hydrolysis of *o*-carboxybenzyl bromide. The isotope effect per D of 1.042 (±0.005) for the *o*-COOH species is insignificantly different than 1.038 (±0.006) for the *o*-COO^- species. Although there is a 15 000-fold rate difference between the protonated and ionized *o*-carboxyl substrates, the almost identical α-deuterium isotope effects indicate that these two states of ionization go through strikingly similar transition states (A and B). This is outlined in Figure 2. The nearly constant magnitude of the α-deuterium isotope effects, in the

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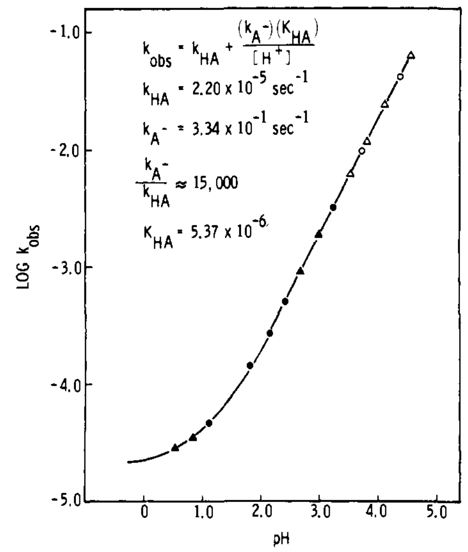

Figure 1. pH-rate profile for the hydrolysis of *o*-carboxybenzyl bromide in 50% aqueous dioxane at 25 °C.

Table I. Hydrolysis of *o*-$COOHC_6H_4CH_2Br/CD_2Br$ in 50% Aqueous Dioxane at 25 °C (μ = 0.50 M, $NaClO_4$)

10^3k_{obsd}, s^{-1} [a]	10^3k_{calcd}, s^{-1} [b]	pH[c]	(k_H/k_D)[d] per D
0.028	0.028	0.560	1.039 (4)
0.034	0.034	0.840	1.045 (4)
0.049	0.046	1.129	
0.164	0.145	1.838	
0.306	0.270	2.141	
0.607	0.506	2.431	
0.996	0.897	2.688	1.043 (2)
1.99	2.10	3.020	1.039 (7)
3.13	3.24	3.254	
6.47	6.20	3.537	1.036 (5)
11.1	9.77	3.735	
11.5	11.5	3.805	1.034 (6)
24.8	23.8	4.122	1.045 (9)
40.8	48.6	4.433	
64.7	59.8	4.524	1.042 (9)

[a] Rate constants obtained by spectrophotometric method. [b] Calculated using $k_{HA} = 2.20 \times 10^{-5}\ s^{-1}$, $k_{A^-} = 0.343\ s^{-1}$, and pK_a = 5.27 and eq 1 in text. [c] Meter readings of apparent pH in 50D containing either dilute $HClO_4$ or formate buffers. [d] Average standard deviation (in parentheses) of four to six determinations, e.g., 1.039 (4) = 1.039 ± 0.004.

region of 1.04 for a bromide leaving group, indicates that the change in force constants attending the formation of the transition state is similar in A and B (Figure 2).

Although much work has been reported for the benzyl system[7] including α-deuterium, carbon-14, and leaving group isotope effects and solvent effects, controversial mechanistic questions regarding mixed S_N1-S_N2 schemes and ion-pair schemes[8] still require experimental attention.

Summary

We believe that the α-deuterium isotope effects of 1.042 and 1.038 for *o*-COOH and *o*-COO^- substrates, respectively, are in the range expected for S_N2 reactions.[9] The remarkable similarity of the isotope effects for *o*-COOH and *o*-COO^- groups, which differ enormously in their reactivity, provides important evidence that the hydrolysis of *o*-carboxybenzyl bromide is an intramolecular displacement reaction.

Experimental Section

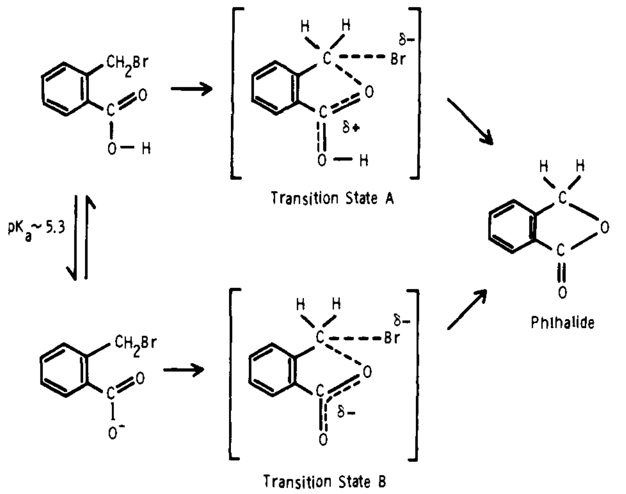

Figure 2. Suggested transition states for neighboring groups, COOH (A) and COO^- (B), in the hydrolysis of *o*-carboxybenzyl bromide.

Table II. Hydrolysis of $RC_6H_4CH_2Br$ in 50% Aqueous Dioxane at 25 °C (μ = 0.50 M, $NaClO_4$)

substrate R	k_{obsd}, s^{-1}	k_{rel}
H	7.20×10^{-6}	1.0
o-COOH	2.20×10^{-5}	3.8
o-COO^-	3.34×10^{-1}	46 000
p-COOH[a]	1.6×10^{-6}	0.3
p-COO^- [b]	1.33×10^{-5}	1.8

[a] Approximate value; this is an extremely slow hydrolysis and less than 50% of the reaction was followed spectrophotometrically at 250 nm. [b] In 50% aqueous dioxane containing 0.005 M NaOH and no $NaClO_4$.

Materials. Benzyl bromide (Pfaltz and Baur, Inc.) was redistilled under reduced pressure as needed. A commercial (Aldrich) sample of *p*-carboxybenzyl bromide was recrystallized from $CHCl_3$, mp 225–226 °C (lit.[3a] 223 °C).

***o*-Carboxybenzyl Bromide.** In a 25-mL ampule were placed 1.05 g of commercial (Aldrich) phthalide and 10 mL of $CHCl_3$. The solution was saturated with dry HBr at 0–5 °C. The sealed ampule was heated at 60 °C for nearly 4 days when crystalline *o*-carboxybenzyl bromide separated. The crystals were filtered and recrystallized from $CHCl_3$. Yield of product was 1.29 g (77%), mp 148–149 °C (lit.[3a] 146 °C), for which ^1H NMR showed ($CDCl_3/Me_4Si$) δ 5.0 (s, 2 H), 7.2–8.1 (m, 4 H), and 11.1 (s, 1 H).

***o*-Carboxybenzyl-α,α-d_2 Bromide.** The procedure of Bailey and Johnson[10] was used to reduce phthalic anhydride using $NaBD_4$ (Stohler Chemical Co.) in DMF at ambient temperature. From 10 mmol of phthalic anhydride and 12 mmol of $NaBD_4$ in 15 mL of DMF (CaH_2 dried) was obtained 7.3 mmol (73%) of distilled product (bp 105–108 °C, ca. 0.2 Torr). The ^1H NMR ($CDCl_3/Me_4Si$) of deuterated phthalide showed a signal at δ 5.3 (methylene protons) which corresponded to about 10% undeuterated phthalide.

Using a procedure similar to the one used for *o*-carboxybenzyl bromide, from 6 mmol of deuterated phthalide was obtained a 55% yield of *o*-$COOHC_6H_4CD_2Br$, mp 146–147 °C. The ^1H NMR spectrum of this compound indicated ca. 90% deuteration. Deuterium analysis[11] showed 88% deuteration. Mass spectral results gave a total 88.9% deuteration with the following deuterium distribution: 79.5% *o*-$COOHC_6H_4CD_2Br$, 18.9% *o*-$COOHC_6H_4CHDBr$, and 1.6% *o*-$COOHC_6H_4CH_2Br$.

Reagent grade *p*-dioxane (J. T. Baker & Co.) was redistilled as needed from freshly cut sodium metal. Deionized, glass-distilled water was used to prepare aqueous dioxane stock solutions. Reagent grade anhydrous $NaClO_4$ (Ventron) was used.

Kinetics. Spectrophotometric Method. A Gilford 2400-2 UV-vis spectrophotometer with thermostated cell compartment at 25 ± 0.2 °C was used. In general, the kinetics of hydrolysis of benzyl bromide and *o*- and *p*-carboxybenzyl bromides were followed by monitoring the disappearance of reactants at appropriate wavelengths in the UV region. For benzyl bromide the reaction was followed at 230 nm and for the other two substrates λ was 250 nm. The rate constants reported in Table II for benzyl and *p*-carboxybenzyl bromides are average values of at least three sets, each a set of triplicate runs.

In a typical determination of a set of α-D isotope effects, 10–15 μL of dioxane stock solution of substrate was added to each of three cells containing 3 mL of 50D ($\mu = 0.50$ M, $NaClO_4$) solution preequilibrated at 25 °C. Initial substrate concentration was on the order of 10^{-5}–10^{-4} M. To obtain an isotope effect, the rates of either two H's and one D or two D's and one H were determined concurrently. The hydrolysis reaction was followed for at least 8 half-lives. The rate constants were obtained using a nonlinear least-squares regression analysis. Duplicate rate constants within a set (2 H's or 2 D's) were averaged and the α-D isotope effect for the set was then calculated. Isotopic correction applied to the observed isotope effects was based on the mass spectral results mentioned earlier. From the deuterium distribution in *o*-carboxybenzyl-α,α-d_2 bromide, it can be shown that $(k_D/k_H)_{obsd} = 0.795\chi^2 + 0.89\chi + 0.016$ where $\chi = (k_{HD}/k_{H_2})$. Thus, the α-D isotope effect per D is shown to be $(k_{H_2}/k_{HD}) = 1/\chi$. The isotope effects listed in Table I are the average of four to six such determinations.

Kinetics. pH Method. A Radiometer pH-stat assembly was used. In these experiments, the initial concentration of *o*-carboxybenzyl bromide was on the order of 1–2 mM. In a typical procedure, 5 mL of buffered solvent was placed in a container maintained at 25 ± 0.2 °C. The end-point pH was set at the apparent initial pH value of the solvent. To the solvent was added 100 μL of a stock solution of the substrate and the HBr produced was titrated against 0.10 or 0.20 M NaOH. Rate constants were determined by nonlinear regression analysis of the titrimetric data for each kinetic run. Rate constants obtained by this method were in excellent agreement with the data by the spectrophotometric method.

pK_a Determinations. In a typical run using a radiometer pH-stat assembly, 100 μL of 0.20 M dioxane solution of acid was added to 10 mL of 50D ($\mu = 0.50$ M, $NaClO_4$) at 25 °C and titrated potentiometrically with 0.20 M NaOH. For each compound six determinations gave the following pK_as: 5.52 (±0.05), benzoic acid; 5.53 (±0.06), *o*-toluic acid; 5.58 (±0.05), *p*-toluic acid; 5.22 (±0.02), *p*-carboxybenzyl bromide acid. From these pK_a values, the pK_a of *o*-carboxylbenzyl bromide was estimated to be 5.27.

Oxygen-18 Tracer Experiments. All transfers were carried out in a drybox under nitrogen. In a 5-mL ampule were placed 250 μL of 0.1 M HCOOH–0.1 M HCOONa buffer, 500 μL of *p*-dioxane, and 250 μL of 20 excess atom % $H_2{}^{18}O$. To the solution was added 52 mg of anhydrous $NaClO_4$. (The apparent pH of an identically prepared $H_2{}^{16}O$ solution was 4.40.) To the ^{18}O-enriched 50D was added 15 mg of *o*-$COOHC_6H_4CH_2Br$. The sealed ampule was placed in a water bath at 25 °C for 1 h. The solid product obtained by ether extraction was sublimed under reduced pressure. Yield of phthalide was 7.6 mg (81%). Mass spectral analysis of the product showed 0 ± 2% incorporation of oxygen-18.

In another experiment at low pH (apparent pH of 0.56), 200 μL of 2 M $HClO_4$ solution ($H_2{}^{16}O$) was added to 500 μL of dioxane and 300 μL of $H_2{}^{18}O$. After addition of 12 mg of $NaClO_4$ and 17 mg of substrate, the sealed ampule was thermostated at 25 °C for 10 half-lives (~70 h). The yield of sublimed product was 8.0 mg (76%). Mass spectral results showed 0 ± 2% oxygen-18 incorporation in phthalide.

Oxygen-18 Control Experiment with *p*-$OCH_3C_6H_4CH_2Br$. In a dry 5-mL ampule were placed 800 μL of *p*-dioxane, 80 μL of $H_2{}^{16}O$, and 120 μL of $H_2{}^{18}O$. To the solvent was added 136 mg of *p*-methoxybenzyl bromide. The sealed ampule was thermostated at 25 °C for 10 half-lives (~8 h). The product was extracted into ether and the dried ether solution was evaporated under nitrogen. Yield of distilled *p*-methoxybenzyl alcohol was 84 mg (90%). Mass spectral analysis of this product showed 10 ± 2% oxygen-18 incorporation. Expected oxygen-18 incorporation is 12%.

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References and Notes

(1) The mass spectrometry work was carried out at the Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, Md. 21205. The work at Johns Hopkins was supported by NIH Grant GM-21248.

(2) (a) G. Kohnstam and D. L. H. Williams in "The Chemistry of Carboxylic Acids and Esters", S. Patai, Ed., Interscience, New York, 1969, Chapter 16, pp 809–820; (b) M. L. Bender in "Mechanisms of Homogeneous Catalysis from Protons to Proteins", Wiley, New York, 1971, Chapter 9, pp 297–304.

(3) (a) A. Singh, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **84**, 1179 (1962); (b) L. Chauffe, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **31**, 3758 (1966); (c) L. Chauffe and M. K. Priebat, *ibid.*, **41**, 3914 (1976).

(4) (a) V. J. Shiner, Jr., and R. C. Seib, *J. Am. Chem. Soc.*, **98**, 862 (1976). (b) For an excellent discussion of deuterium isotope effects in solvolytic reactions, see V. J. Shlner, Jr., in "Isotope Effects in Chemical Reactions", C. J. Collins and N. S. Bowman, Eds., Van Nostrand-Reinhold, Princeton, N.J., 1970, pp 115–118, and references cited therein.

(5) (a) V. P. Vitullo and F. P. Wilgis, *J. Am. Chem. Soc.*, **97**, 458, 5616 (1975); (b) V. P. Vitullo and R. J. Capp, *J. Chem. Soc., Chem. Commun.*, 7859 (1978).

(6) (a) D. L. Whalen and A. M. Ross, *J. Am. Chem. Soc.*, **98**, 7859 (1976); (b) D. L. Whalen, A. M. Ross, P. M. Dansette, and D. M. Jerina, *ibid.*, **99**, 5672 (1977).

(7) (a) D. G. Graczyk and J. W. Taylor, *J. Am. Chem. Soc.*, **96**, 3255 (1974); (b) V. F. Raaen, T. Juhlke, F. J. Brown, and C. J. Collins, *ibid.*, **96**, 5928 (1974); (c) K. M. Koshy, R. E. Robertson, and W. M. J. Strachan, *Can. J. Chem.*, **51**, 2958 (1973); (d) A. V. Willi, C. Ho, and A. Ghanbarpour, *J. Org. Chem.*, **37**, 1185 (1972); (e) K. M. Koshy and R. E. Robertson, *J. Am. Chem. Soc.*, **96**, 914 (1974); (f) H. Aromovitch and A. Pross, *Tetrahedron Lett.*, 2729 (1977).

(8) R. S. Sneen, *Acc. Chem. Res.*, **6**, 52 (1972).

(9) Unpublished results in our laboratory (J. J. Grawbowski and S. Sridharan) suggest that less than 1.005 to 1.07 (per D) α-deuterium isotope effects can be observed for the S_N2 reaction of benzyl and/or *p*-methoxybenzyl bromide with various nucleophiles in aqueous dioxane solvent. This work will be published shortly.

(10) D. M. Bailey and R. F. Johnson, *J. Org. Chem.*, **35**, 3574 (1970).

(11) Deuterium analysis was done by Mr. Josef Nemeth, University of Illinois, Urbana, Ill. 61801.