preparative GLC (gas chromatography gave benzyl-α,α-d_2 alcohol identified by NMR).

Acknowledgment. We warmly thank Organic Reactions, Inc., and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for grants which supported this work.

Registry No.—Isatoic anhydride, 118-48-9; *tert*-butyl anthranilate, 64113-91-3; diphenylmethane, 101-81-5; deuterated diphenylmethane, 20389-18-8; α,α-diphenylacetophenone, 1733-63-7; benzaldehyde, 100-52-7; *tert*-butyl benzoate, 774-65-2; benzaldehyde-*d*, 3592-47-0; benzyl-α,α-d_2 alcohol, 21175-64-4; 2-carboxybiphenyl, 947-84-2; fluorene, 86-73-7; acetonitrile, 75-05-8; (*E*)-cinnamonitrile-β-*d*, 64113-90-2; (*Z*)-cinnamonitrile-β-*d*, 64113-89-9; deuterated chlorodiphenylmethane, 778-23-40.

References and Notes

(1) D. J. Cram, B. Rickborn, and G. R. Knox, *J. Am. Chem. Soc.*, **82**, 6412 (1960).

(2) G. A. Russell, E. Janzen, H. Becker, and F. Smertowski, *J. Am. Chem. Soc.*, **84**, 2652 (1962).

(3) A. Schriesheim and C. A. Rowe, *J. Am. Chem. Soc.*, **84**, 3160 (1962).

(4) T. J. Wallace, J. E. Hofmann, and A. Schriescheim, *J. Am. Chem. Soc.*, **85**, 2739 (1963).

(5) C. A. Buehler and D. E. Pearson, *Chem. Rev.*, **74**, 45 (1974).

(6) M. Szwarc, Ed., "Ions and Ion Pairs in Organic Reactions", Wiley-Interscience, New York, N.Y., 1972.

(7) See: J. Smid, "Spectrophotometric Studies of Ion Pair Equilibria", p 85 in ref 6.

(8) D. H. Hunter, W. Lee, and S. K. Sim, *J. Chem. Soc., Chem. Commun.*, 1018 (1974). D. H. Hunter and C. A. Perry, *Synthesis*, 37 (1977).

(9) D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).

(10) R. A. Bartsch, *Acc. Chem. Res.*, **8**, 239 (1975).

(11) M. J. Maskornick, *Tetrahedron Lett.*, 7797 (1972).

(12) D. J. Cram, J. C. Mateos, F. Hanck, A. Langemann, K. R. Kopecky, W. D. Nielsen, and J. Allinger, *J. Am. Chem. Soc.*, **81**, 5774 (1959).

(13) (a) Typical solubilities for potassium *tert*-butoxide (in g/100 g of solvent at 25 °C) are given by L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, 911 (1967): hexane (0.27), toluene (2.27), ether (4.34), *tert*-butyl alcohol (17.80), and tetrahydrofuran (25.00). (b) We have found that the solubility of potassium *tert*-butoxide in benzene at 25 ± 2 °C is 1.4 ± 0.2 g/100 g.

(14) (a) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 581 (1973). (b) R. A. Olofson and C. M. Dougherty, *ibid.*, **95**, 582 (1973). (c) R. A. Olofson, K. D. Lotts, and G. N. Barber, *Tetrahedron Lett.*, 3779 (1976). (d) G. N. Barber and R. A. Olofson, *ibid.*, 3783 (1976). (e) R. A. Olofson, K. D. Lotts, and G. N. Barber, *ibid.*, 3381 (1976).

(15) (a) A. L. Huang and S. S. Si Hoe, "Vistas in Free Radical Chemistry", W. A. Waters, Ed., Pergamon Press, New York, N.Y., 1959, p 245. (b) N. A. Milas, *J. Am. Chem. Soc.*, **53**, 221 (1931).

(16) P. T. Lansbury and V. A. Pattison, *J. Org. Chem.*, **27**, 1933 (1962).

(17) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).

(18) W. P. Weber and G. W. Gokel, "Phase Transfer Catalysis in Organic Synthesis", Springer-Verlag, Berlin, 1977.

(19) G. W. Gokel and H. D. Durst, *Synthesis*, 168 (1976).

(20) U.S. Patent 3 126 631; *Chem. Abstr.*, **60**, 13195 (1964).

(21) R. P. Staiger and E. B. Miller, *J. Org. Chem.*, **24**, 1214 (1959).

(22) (a) M. R. V. Sahyun and D. J. Cram, "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N.Y., 926 (1973). (b) S. O. Lawesson and N. C. Yang, *J. Am. Chem. Soc.*, **81**, 4230 (1959). (c) J. E. Shaw, D. C. Kunerth, and S. B. Swanson, *J. Org. Chem.*, **41**, 732 (1976).

(23) D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.*, **96**, 2252 (1974).

(24) G. W. Gokel, H. M. Gerdes, and N. W. Rebert, *Tetrahedron Lett.*, 653 (1976).

(25) (a) B. Dietrich and J.-M. Lehn, *Tetrahedron Lett.*, 2552 (1973). (b) See ref 189 in G. W. Gokel and H. D. Durst, *Synthesis*, 168 (1976). (c) E. Alneri, G. Bottaccio, and V. Carletti, *Tetrahedron Lett.*, 2117 (1977).

(26) (a) P. G. Gassman, P. K. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976), and references therein. (b) G. W. Kenner, M. J. T. Robinson, C. M. B. Taylor, and B. R. Webster, *J. Chem. Soc.*, 1756 (1962).

(27) (a) C. Kruger, *J. Organomet. Chem.*, **9**, 125 (1967). (b) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **33**, 3402 (1968). (c) D. N. Crouse and D. Seebach, *Chem. Ber.*, **101**, 3113 (1968). (d) I. Pattison, K. Wade, and B. K. Wyatt, *J. Chem. Soc.*, 837 (1968). (e) T. Kametani, Y. Yamaki, and K. Ogasawara, *Yakugaku Zasshi*, **89**, 154 (1969) [*Chem. Abstr.*, **70**, 106342y (1969)]. (f) A. Uchida, S. Saito, and S. Matsuda, *Bull. Chem. Soc. Jpn.*, **42**, 2989 (1969). (g) T. P. Vishnavakova and A. A. Koridze, *Zh. Obshch. Khim.*, **39**, 210 (1969). (h) A. Uchida, A. Doyama, and S. Matsuda, *Bull. Chem. Soc. Jpn.*, **43**, 963 (1970). (i) R. Das and C. A. Whikie, *J. Am. Chem. Soc.*, **94**, 4555 (1972). (j) K. Takahashi, K. Sasaki, H. Tanabe, Y. Yamada, and H. Ida, *J. Chem. Soc. Jpn., Chem. Ind. Chem.*, 2347 (1973). (k) W. Stilz and H. Pommer, Ger. Off. 1 108 208 [*Chem. Abstr.*, **56**, 11422e (1962)]. (l) G. P. Schiemenz and H. Engelhard, *Chem. Ber.*, **95**, 195 (1962). (m) J. Ghosez, *Bull. Soc. Chim. Belg.*, **41**, 477 (1932); see also: J. G. Krause and S. Shaikh, *Synthesis*, 502 (1975), and J. J. Louvar and A. K. Sparks, Ger. Off., 2 041 563 [*Chem. Abstr.*, **75**, 199897 (1971)].

(28) S. A. DiBiase, G. W. Gokel, and B. A. Lipisko, *Tetrahedron Lett.*, 3495 (1976).

(29) E. Elkik, H. Assadi-Far, and H. Normant, *C. R. Hebd. Seances Acad. Sci.*, 267 (1968).

(30) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Am. Chem. Soc.*, **89**, 946 (1967).

Base-Catalyzed β-Elimination Reactions. 7. Elimination from 4-(Para-substituted-phenoxy)-2-oxobutanoic Acids

James M. Hilbert and Leo Fedor*

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260

Received August 22, 1977

Elimination of para-substituted phenoxides from 4-(para-substituted-phenoxy)-2-oxobutanoic acids in aqueous solution is catalyzed by imidazole, morpholine, diethanolamine, and *N,N*-dimethylethanolamine. The dependence of the pseudo-first-order rate constant on amine concentration is nonlinear, with an initial line of large slope at low amine concentration which changes to a line of smaller slope at high amine concentration. The existence of a carbanion intermediate in the reaction is supported by the result that α-hydrogen exchange at high amine concentration is faster than elimination. These findings, coupled with the results of analysis of Hammett ρ' values for various steps of the elimination reaction catalyzed by morpholine, lead us to conclude that elimination proceeds via spontaneous decomposition of enolates and general-base-catalyzed decomposition of enols.

A considerable body of evidence indicates that many base-catalyzed β-elimination reactions proceed via carbanion intermediates.[1-6] For example, under the experimental conditions employed, β-elimination of para-substituted phenoxides from 4-(para-substituted-phenoxy)-2-butanones is adequately described by the minimal mechanism of Scheme I.[5]

Many biochemical reactions such as aldolization,[7-9] decarboxylation,[10] carboxylation,[8] and elimination[11-13] are thought to occur via proton transfer to form a carbanion intermediate from α-keto acid substrates, and our own interest in carbanion chemistry is related in part to our desire to understand enzyme catalysis. In order to better understand the chemistry of elimination reactions, specifically in compounds capable of stabilizing enols, and to develop potential suicide substrates[14-16] for those enzymes which utilize α-keto acid

Scheme I

$$\mathrm{ArOCH_2CH_2COCH_3} \xrightleftharpoons[k_2,\ \mathrm{BH}]{k_1,\ \mathrm{B}} \mathrm{ArOCH_2CHCOCH_3}^-$$

$$\xrightarrow{k_3} \mathrm{CH_2{=}CHCOCH_3} + \mathrm{ArO^-}$$

substrates, we synthesized four 4-(para-substituted-phenoxy)-2-oxobutanoic acids (X = H (1), CH_3 (2), CH_3O (3), and Cl (4)) and studied their base-catalyzed elimination reactions (eq 1). This study showed that β-elimination reactions are facile, that elimination occurs via general-base-catalyzed proton transfer to form carbanions, and that the reaction is necessarily more complex than the simple E1cB reaction mechanism of Scheme I.

$$p\text{-X-}C_6H_4OCH_2CH_2COCO_2^- \rightarrow p\text{-X-}C_6H_4OH + CH_2{=}CHCOCO_2^- \quad (1)$$

Experimental Section

Apparatus. The apparatus used for collection of rate data was previously described.[5] Calculations were performed on either a Hewlett Packard 2700 calculator using the first-order kinetics data and linear regression programs from the program library provided or on a Hewlett Packard HP 25 calculator. The plots of the pseudo-first-order rate constants vs. concentration of base were fitted to curves by the CDC 6400 computer of the State University of New York at Buffalo, using the NLIN 2 curve-fitting program from the program library of the State University of New York at Buffalo. NMR spectra were taken on either Varian A-60 or T-60 instruments with Me_4Si as an internal standard, and the proton signals are reported in δ values downfield from Me_4Si. Melting points were taken in open capillary tubes in a Mel-Temp apparatus and are uncorrected.

Reagents. All inorganic reagents were Fisher Certified ACS Grade, except D_2O (99.8% D), Stohler Isotope Chemicals, DCl (+99% D), and KOD (98% D), Aldrich Chemical Co. All organic reagents were purchased from Aldrich Chemical Co. Tap-distilled water was redistilled through a Corning aGla still before use.

Kinetics. All reactions were carried out at 30 ± 0.1 °C in aqueous solution and at an ionic strength of 1.0 M maintained with KCl. The pH of solutions was measured and found to be constant, ±0.02 pH unit, for all serial dilutions of constant catalytic buffer ratio. In addition, the pH of reaction solutions was taken after each run, and the pH change never exceeded 0.08 pH unit; pH drift occurred in the very dilute buffers. Reactions were run under pseudo-first-order conditions with substrate concentration $\sim 2 \times 10^{-4}$ M. The reactions were initiated by addition of the substrate in ethanol to amine or hydroxide solutions, except in cases where the reaction proved to be too fast to monitor by these conditions. For reactions which had pseudo-first-order rate constants greater than $\sim 8.5\ \text{min}^{-1}$, 3 mL of the amine or hydroxide solution, which had been equilibrated at a temperature of 30 °C in a constant-temperature bath, was rapidly added to a cuvette containing the substrate using an Oxford macro-transfer pipet. Reactions were monitored by following the appearance of phenol or phenoxide, depending on the pH, at the following wavelengths (compound, phenol, phenoxide): 4-phenoxy-2-oxobutanoic acid (1), 278, 286 nm; 4-(*p*-cresoxy)-2-oxobutanoic acid (2), 286, 296 nm; 4-(*p*-anisoxy)-2-oxobutanoic acid (3), 304, 309 nm; 4-(*p*-chlorophenoxy)-2-oxobutanoic acid (4), 294, 310 nm.

Products. The course of the reaction of each of the compounds 1–4 with 0.04 M KOH was scanned from 210 to 410 nm. In each case, the appearance of para-substituted phenoxides was confirmed by spectral comparisons using authentic para-substituted phenols. Relatively strong absorption of phenoxides coupled with the presumed instability of 2-oxobutenoic acid[2] prevented detection of this acid by UV spectroscopy. Reaction of 4-(*p*-chlorophenyl)-2-oxobutanoic acid with 0.04 M KOD in D_2O was monitored by NMR spectrometry. The reaction product showed an absorption at δ 6.38 which we attribute to vinyl protons in an α,β-unsaturated carbonyl system. A signal at δ 6.38 was found for the unstable pyrolysis products of 4-*N*,*N*-diethylamino-2-oxobutanoic acid.[17] The amount of *p*-cresoxide ion formed on reaction of 2.5×10^{-4} M 2 in 0.04 M KOH was quantitated. After reaction, the concentration of *p*-cresoxide ion was 2.58×10^{-4} M, calculated from the absorbance (0.703) at 296 nm and the molar extinction coefficient $2.73 \times 10^3\ \text{M}^{-1}\ \text{cm}^{-1}$, which was obtained from the data of Lang.[18]

Syntheses. Diethoxyacetic acid, bp 81 °C (0.3 mm), was prepared in 83% yield by the method of Moffett.[19]

Benzyl Diethoxyacetate. A solution of saturated aqueous K_2CO_3 was added dropwise to 22.5 g (0.15 mol) of diethoxyacetic acid until no more CO_2 was evolved, and the pH was between 7.5 and 8. The water was then evaporated in a rotary evaporator, and the carboxylate salt was added to 28.9 g (0.228 mol) of benzyl chloride in 300 mL of dimethylformamide. The mixture was heated to 90 °C with stirring for 1 h. Benzene was added to the cooled mixture which was then washed with three portions of water. The organic solution was collected and dried ($MgSO_4$), and benzene and DMF were removed on a rotary evaporator. Distillation gave a forerun of benzyl chloride followed by benzyl diethoxyacetate: yield 37.5 g (76%); bp 99–101 °C (0.05 mm); NMR ($CDCl_3$) 1.22 (t, 6 H), 3.64 (q, 4 H), 4.91 (s, 1 H), 5.19 (s, 2 H), 7.31 (s, 5 H).

2-Carbobenzoxy-1,3-dithiane. The method of Eliel[20] was used. A solution of 4.6 g (42.4 mmol) of 1,3-propanedithiol and 13.6 g (57.1 mmol) of benzyl diethoxyacetate in 50 mL of $CHCl_3$ was added dropwise to a refluxing solution of 12 g (85.2 mmol) of boron trifluoride etherate in 100 mL of $CHCl_3$. The solution was refluxed for 0.5 h, cooled, and washed with 80 mL of H_2O, 80 mL of 10% aqueous K_2CO_3, and then with two 80-mL portions of H_2O. The $CHCl_3$ solution was dried ($MgSO_4$) and $CHCl_3$ removed in a rotary evaporator, leaving crystals which were recrystallized twice from hexane: yield 9 g (62%); mp 72–75 °C; NMR ($CDCl_3$) 1.79–2.32 (m, 2 H), 2.47 (t, 1 H), 2.55 (t, 1 H), 3.41 (m, 2 H), 4.25 (s, 1 H), 5.25 (s, 2 H), 7.41 (s, 5 H).

2-(β-Para-substituted-phenoxy)ethyl-2-carbobenzoxy-1,3-dithianes. Para-substituted bromophenetoles, with the exception of β-bromophenetole (Aldrich Chemical Co.), were prepared by the method of Adams and Thol[21] (compound, mp, yield): *p*-CH_3, 48–50 °C, 38%; *p*-CH_3O, 49–50 °C, 51%; *p*-Cl, 40–41 °C, 32%. The following general method was employed using 10–60 mmol quantities of the β-bromophenetole. a solution of 2-carbobenzoxy-1,3-dithiane in DMF/benzene (3:1) was added dropwise to a stirred suspension of an equimolar quantity of NaH in 150 mL of DMF/benzene (3:1) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then a 1.2 mol excess of the desired para-substituted β-bromophenetole in a solution of DMF/benzene (3:1) was added dropwise with stirring . The temperature of the mixture was allowed to rise to 25 °C, and the mixture was stirred for 15 h at 25 °C. Benzene was then added to the mixture, and the organic layer was washed three times with water. The solvent was removed by rotary evaporation, and the product was crystallized and recrystallized from hexane. Melting points and yields are as follows: *p*-H, 55–58 °C, 43%; *p*-CH_3, 50–53 °C, 55%; *p*-CH_3O, 63–64 °C, 59%; *p*-Cl, 55–56 °C, 59%. NMR ($CDCl_3$): *p*-H 1.87 (t, 2 H), 2.56 (m, 4 H), 2.86–3.53 (dtd, 2 H), 4.16 (t, 2 H), 5.16 (s, 2 H), 6.46–7.23 (m, 5 H), 7.26 (s, 5 H); *p*-CH_3 2.02 (m, 2 H), 2.35 (s, 3 H), 2.67 (m, 2 H), 3.14–3.66 (dtd, 2 H), 4.3 (t, 2 H), 5.41 (s, 2 H), 6.85–7.4 (dd, 4 H), 7.6 (s, 5 H); *p*-CH_3O 1.89 (m, 2 H), 2.55 (m, 4 H), 2.96–3.54 (dtd, 2 H), 3.72 (s, 3 H), 4.15 (t, 2 H), 5.21 (s, 2 H), 6.76 (s, 4 H), 7.34 (s, 5 H); *p*-Cl 1.87 (m, 2 H), 2.6 (m, 4 H), 2.9–3.7 (dtd, 2 H), 4.12 (t, 2 H), 5.2 (s, 2 H), 6.73 (d, 2 H), 7.15 (d, 2 H), 7.31 (s, 5 H).

Benzyl 4-(Para-substituted-phenoxy)-2-oxobutanoates. Very specific conditions, similar to those of Corey and Erickson,[22] were employed. 2-(β-Para-substituted-phenoxy)ethyl-2-carbobenzoxy-1,3-dithiane (20 mmol) in 5 mL of an acetone solution was added dropwise to a stirred suspension of *N*-chlorosuccinimide and silver nitrate (1:4:4.5 mol ratio). The addition was made as rapidly as possible while maintaining the reaction temperature at 25 °C by the use of an ice bath. After the addition, the mixture was stirred for 5 min at 25 °C; longer times tended to give lower yields. The reaction was stopped by cooling the reaction mixture to 0 °C and then adding, at 1-min intervals, 5 mL each of saturated $NaHSO_3$, 10% $NaHCO_3$, H_2O, and saturated NaCl. Hexane/CH_2Cl_2 (1:1) was added, and the mixture was filtered through Celite. The organic phase was separated and dried ($MgSO_4$), and the solvent was flash-evaporated to give benzyl 4-(para-substituted-phenoxy)-2-oxobutanoates, which were crystallized and recrystallized from hexane/CS_2 (9:1). Melting points and yields are as follows: *p*-H, 49.5–51 °C, 22%; *p*-CH_3, 66–67 °C, 26%; *p*-CH_3O, 45–46°C, 11%; *p*-Cl, 82.5–84.5 °C, 34%. NMR: *p*-H 3.33 (t, 2 H), 4.37 (t, 2 H), 5.43 (s, 2 H), 6.88–7.55 (m, 5 H), 7.6 (s, 5 H); *p*-CH_3 2.33 (s, 3 H), 3.32 (t, 2 H), 4.33 (t, 2 H), 5.36 (s, 2 H), 6.75–7.3 (q, 4 H), 7.47 (s, 5 H); *p*-CH_3O 3.18 (t, 2 H), 3.68 (s, 3 H), 4.16 (t, 2 H), 5.19 (s, 2 H), 6.71 (s, 4 H), 7.26 (s, 5 H); *p*-Cl 3.31 (t, 2 H), 4.29 (t, 2 H), 5.34 (s, 2 H), 6.72–7.36 (q, 4 H), 7.45 (s, 5 H).

4-(Para-substituted-phenoxy)-2-oxobutanoic Acids 1–4. Benzyl 4-(para-substituted-phenoxy)-2-oxobutanoates (10 mmol) were dissolved in 50 mL of ethyl acetate and hydrogenolyzed over Pd/C at 2.75 atm for 4 h. Solvent was removed by flash evaporation following filtration of the reaction solution through Celite. The residues 1–4 were crystallized from CCl_4 and recrystallized from hexane/benzene (7:3) to give the corresponding acids.

1 (*p*-H): 59% yield; mp 83–85 °C; NMR 3.5 (t, 2 H), 4.49 (t, 2 H), 6.92–7.75 (m, 5 H), ~8.4 (s, 1 H).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; O, 32.96. Found: C, 61.84; H, 5.17; O, 33.05.

2 (*p*-CH_3): 45% yield; mp 96–98 °C; NMR 2.30 (s, 3 H), 3.39 (t, 2 H), 4.34 (t, 2 H), 6.98 (q, 4 H), 8.4 (s, 1 H).

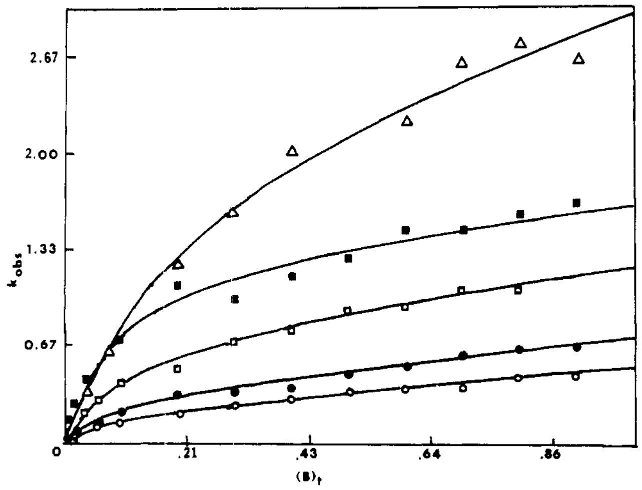


Figure 1. Plot of the pseudo-first-order rate constant, k_{obsd}, vs. the total concentration of morpholine (M) for reactions of 4-*p*-cresoxy-2-oxobutanoic acid (**2**) with that amine: ○, pH 8.0; ●, pH 8.26; □, pH 8.63; ■, pH 8.93; △, pH 9.26.

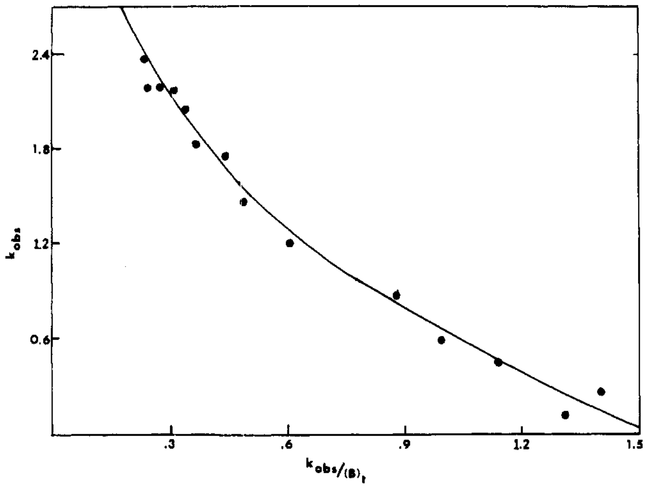


Figure 2. Eadie–Hofstee type plot of the pseudo-first-order rate constant, k_{obsd}, vs. k_{obsd}/[Morpholine]$_{total}$ for reactions of 4-phenoxy-2-oxobutanoic acid (**1**) with that amine at pH 8.92.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.44; H, 5.82; O, 30.74. Found: C, 63.52; H, 5.73; O, 30.59.

3 (*p*-CH$_3$O): 40% yield; mp 99–102 °C; NMR 3.23 (t, 2 H), 3.71 (s, 3 H), 4.27 (t, 2 H), 6.76 (q, 4 H), ~8.4 (s, 1 H).

Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.41; O, 35.68. Found: C, 58.77; H, 5.47; O, 35.67.

4 (*p*-Cl): 68% yield; mp 102–104 °C; NMR 3.36 (t, 2 H), 4.28 (t, 2 H), 6.66–7.38 (q, 4 H), ~8.4 (s, 1 H).

Anal. Calcd for $C_{10}H_9ClO_4$: C, 52.53; H, 3.98; O, 27.99. Found: C, 52.49; H, 4.35; O, 28.63.

Results

4-(Para-substituted-phenoxy)-2-oxobutanoic acids **1–4** undergo general-base-catalyzed β-elimination to give para-substituted phenols and 2-oxobutenoic acid (eq 1) in aqueous solutions of amine buffers. Spontaneous elimination at pH 7 was found to be negligible. Plots of the pseudo-first-order rate constants, k_{obsd}, vs. concentration of amine bases were curved, showing a complex dependence of k_{obsd} on the total concentration of amine base, $[B]_t$. The plots appeared to be biphasic, with an initial line of large slope at low $[B]_t$ which changed to a line of smaller slope at high $[B]_t$. A family of these plots obtained using 4-(*p*-cresoxy)-2-oxobutanoic acid (**2**) as the substrate and morpholine as the amine catalyst is shown in Figure 1.[23] A similar change in slope with change in base or acid concentration has been seen for several different reactions;[24–29] including the elimination of water from 9-hydroxy-10-methyl-2-*cis*-decalone. The biphasic curve is indicative of the presence of an intermediate in the reaction, and the change in slope signifies a change in the rate-determining step of the reaction.[25]

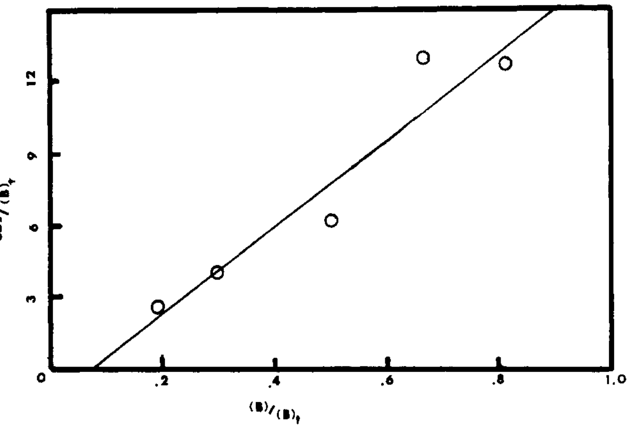


Figure 3. Plot of the pseudo-first-order rate constant, k_{obsd}, divided by the molar concentration of total morpholine vs. the fraction of the base form of morpholine for reactions of 4-*p*-cresoxy-2-oxobutanoic acid (**2**) with 0.01 M morpholine.

The pseudo-first-order rate constants of the reactions were measured up to a total base concentration of 1.0 M, at which concentration the final limiting slope has not been reached and can not be easily determined and verified. It was important to determine whether the final slope had a value of 0 or more. If the final slope were 0, the shape of the k_{obsd} vs. $[B]_t$ plot would be similar to that observed by Fedor and Glave[5] in their study of the elimination of phenols from 4-(para-substituted-phenoxy)-2-butanones and could be described by eq 2, the pseudo-first-order rate equation for a simple E1cB process (Scheme I). A nonzero final slope implies more than one intermediate and/or more than one pathway for decomposition of the intermediate to product, as shown for elimination from 9-hydroxy-10-methyl-2-*cis*-decalone.[6] Two criteria were used to show that the final slopes were greater than 0. First, an Eadie–Hofstee type plot of k_{obsd} vs. $k_{obsd}/[B]_t$ will give a straight line according to eq 3, where fr_A is the fraction of free acid, for a biphasic curve with a final slope of 0. It was found that for elimination from **1** to **4** the Eadie–Hofstee plots were curved as shown typically in Figure 2. Second, a computer fit of the data obtained for reactions of **1–4** run at any constant pH to a curve described by eq 4 could be made. This equation describes the biphasic curves of Figure 1. The parameters *p*, *q*, and *r* are combinations of constants. The initial limiting slope, when values of $[B]_t$ are very small such that $p[B]_t \gg q[B]_t^2$, is equal to *p* and the final limiting slope, when values of $[B]_t$ are large such that $r[B]_t \gg 1$, is equal to q/r. Also, plots (not shown) of $k_{obsd}/[B]_t$ vs. $[B]_t$ (eq 5) are hyperbolic with finite, nonzero limits.[44]

$$k_{obsd} = k_1[B]/((k_2/k_3)[BH] + 1) \qquad (2)$$

$$k_{obsd} = k_1k_3K_a/k_2a_H - (k_3/k_2fr_A)(k_{obsd}/[B]_t) \qquad (3)$$

$$k_{obsd} = (p[B]_t + q[B]_t^2)/(r[B]_t + 1) \qquad (4)$$

$$k_{obsd}/[B]_t = (p + q[B]_t)/(r[B]_t + 1) \qquad (5)$$

We take the above results to show that the curves exemplified by those of Figure 1 are indeed biphasic and that the final slopes have values greater than 0. Table I lists values of *p*, *q*, and *r* for the second-order plots of eq 4 for reactions of **1–4** with amines of this study. These parameters were obtained by computer fits of the data to eq 5.

Table I. Kinetics Data According to Equation 4 for Reactions of 1-4 in Aqueous Solutions of Amine Buffers[a]

Amine	Substrate	Registry no.	pH	Fraction of free base (fr_B)	p	q	r	Final slope[b]	SE[c]
Morpholine	1 (H)	64114-05-2	7.99	0.190	2.72	3.33	9.88	0.737	7.17×10^{-3}
			8.26	0.304	3.98	1.75	5.90	0.296	2.75×10^{-2}
			8.62	0.500	7.20	3.77	5.5	0.687	4.20×10^{-2}
			8.93	0.671	15.0	7.02	8.05	0.872	5.33×10^{-2}
			9.26	0.814	12.4	4.03	3.59	1.12	7.79×10^{-2}
	2 (CH_3)	64114-04-1	8.00	0.193	2.84	4.92	13.5	0.366	1.02×10^{-2}
			8.26	0.304	4.53	5.52	12.7	0.433	2.28×10^{-2}
			8.62	0.500	7.30	5.48	9.40	0.582	2.24×10^{-2}
			8.93	0.671	15.3	6.35	12.0	0.529	7.89×10^{-2}
			9.25	0.810	11.3	5.50	4.61	1.19	1.3×10^{-1}
	3 (CH_3O)	64114-03-0	8.05	0.212	2.08	0.912	4.56	0.200	1.63×10^{-2}
			8.29	0.319	3.25	0.583	3.38	0.172	2.06×10^{-2}
			8.62	0.500	6.60	1.51	4.06	0.373	4.35×10^{-2}
			8.93	0.671	9.26	2.61	4.03	0.648	3.18×10^{-2}
			9.26	0.814	12.6	0.709	2.62	0.271	4.37×10^{-2}
	4 (Cl)	64114-02-9	8.01	0.197	3.59	5.67	6.78	0.836	5.07×10^{-2}
			8.26	0.304	4.47	5.74	3.86	1.49	3.06×10^{-2}
			8.62	0.500	7.90	2.68	2.18	1.23	7.30×10^{-2}
			8.93	0.671	11.2	9.55	3.41	2.80	1.04×10^{-1}
			9.26	0.814	13.9	11.5	2.65	4.36	6.29×10^{-2}
Imidazole	1 (H)		6.50	0.220	0.137	0.130	16.13	0.00804	7.29×10^{-4}
			6.86	0.392	0.169	0.0209	3.71	0.00563	2.93×10^{-2}
			7.05	0.500	0.218	0.219	6.10	0.0359	2.71×10^{-3}
			7.26	0.619	0.308	0.0628	4.69	0.0134	2.12×10^{-3}
			7.70	0.817	0.346	0.0443	2.26	0.0196	3.39×10^{-3}
Imidazole	3 (CH_3O)		7.05	0.500	0.151	0.0503	4.44	0.0113	1.66×10^{-2}
Diethanolamine	1 (H)		8.17	0.183	1.48	6.33	9.9	0.639	1.91×10^{-2}
			8.67	0.415	4.15	12.0	10.25	1.17	4.25×10^{-2}
			8.82	0.500	4.27	8.15	5.65	1.44	4.33×10^{-2}
			9.33	0.764	9.09	3.15	3.86	0.818	1.55×10^{-1}
			9.49	0.824	8.65	0.801	1.26	0.636	1.31×10^{-1}
Dimethylamino-ethanol	3 (CH_3O)		8.81	0.186	10.21	5.02	5.68	0.884	2.49×10^{0}
			9.12	0.319	19.4	8.70	5.46	1.60	1.63×10^{0}
			9.38	0.460	30.6	6.31	4.41	1.43	2.32×10^{0}
			9.76	0.670	44.7	6.15×10^{-9}	2.45	2.52×10^{-9}	1.69×10^{0}
			10.02	0.788	51.8	3.36×10^{-8}	1.93	1.74×10^{-8}	2.04×10^{0}

[a] The concentration range of base is 0.01–1.0 M; 15 k_{obsd} values/pH; 30 °C and μ 1.0 M (KCl). [b] The final slope values are erratic because of the somewhat erratic values of k_{obsd} obtained from the spectrophotometric assay when the absorbance change between 1–4 and the products is small. A single point on the k_{obsd} vs. [B] plot can make a great deal of difference in the parameter values given by the curve-fitting program. Thus, the final slope values are variable, but there are sufficient points to assure that the reported effects, e.g., positive final slopes (Figure 1), ρ (k_1) ~ 0 and ρ (k_4) $> \rho$ (k_3), are real. [c] The values of the parameters p, q, and r were those for which the sum of the squares of the differences between observed and predicted k_{obsd} values were minimized as defined by ϕ, where $\phi = \Sigma^n{}_{i=1}[Y_i - \hat{Y}_i]^2$ and Y_i is k_{obsd} (experimental) and $\hat{Y}_i$ is k_{obsd} (predicted). The standard error of estimate, SE, is $(\phi/(N - K))^{1/2}$, where N is the number of k_{obsd} values and K is the number of constants (4) to be determined; as run, the equation used was $k_{obsd} = (ax + bx^2)/(cx + d)$, and $p = a/d$, $q = b/d$, and $r = c/d$.

The data of Table I show that the initial and final slopes increase with the increasing fraction of free amine (fr_B) (cf. Figure 1), which suggests that general base and not general acid catalysis is present in the limiting cases. For each base, a plot of $k_{obsd}/[B]_t$ vs. fr_B obtained for different pH values was drawn using the k_{obsd} values at 0.01 M $[B]_t$. That value was chosen because it was assumed that at low base concentrations the value of k_{obsd} lies on or near to the initial slope. One of these plots is shown in Figure 3. All plots were linear and had either 0 or small negative intercepts, indicating that the initial slope indeed reflects general-base- and not general-acid-catalyzed processes; the presence of general-acid-catalyzed processes would require positive intercepts in the graphs. Since only general-base catalysis was observed, the equation of the initial line (Figure 1, eq 4) would have the form of eq 6, and any proposed mechanism for the reactions of 1–4 must have a steady-state equation which reduces to eq 6 at very low base concentrations. Similar plots were not made for final slopes because the values of k_{obsd} obtained at the highest $[B]_t$ used (1.0 M) were not on the final slope.

$$k_{obsd}\ (\text{initial}) = k_1 fr_B[B]_t \qquad (6)$$

For hydroxide ion catalysis of elimination, a plot of k_{obsd} vs. a_{OH} for reactions of 4-phenoxy-2-oxobutanoic acid (1) was linear over the limited range of hydroxide activities over which the reaction rates could be monitored (Figure 4). The small intercept in the plot is statistically insignificant. The second-order rate constant for hydroxide ion catalysis was obtained from the slope of the line and is provided in Table II together with those constants for the reactions of 2–4 with one hydroxide ion concentration. Hydroxide ion catalysis was not an important contribution to the elimination reactions of 1–4 in catalytic amine buffer solutions. Values of $k_{obsd} - k_{OH}a_{OH} \simeq k_{obsd}$ for reactions in amine buffer solutions, except for values of k_{obsd} obtained for the lowest base concentration, 0.01 M, at the highest pH of a set; in these cases, the value of $k_{OH}a_{OH}$ was approximately 15% of k_{obsd}. Also, a computer fit of the data to eq 4, with the $k_{OH}a_{OH}$ term appended, invariably gave values of this latter term which were negligible in comparison with the values of the other parameters. Hy-

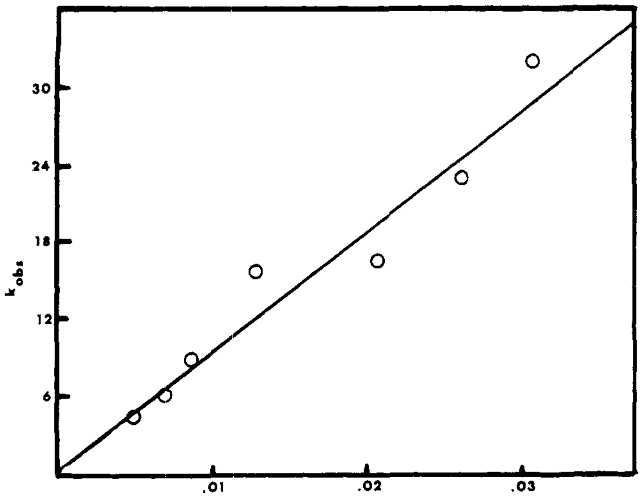


Figure 4. Plot of the pseudo-first-order rate constant, k_{obsd}, vs. the hydroxide activity, K_w/a_H, for reactions of 4-phenoxy-2-oxobutanoic acid (1) with hydroxide ion.

Table II. Rate Data for Hydroxide Ion Catalyzed Elimination Reactions of 1–4

Compd	$a_{OH} \times 10^3$	k_{obsd}, min^{-1}	k_{OH}, M^{-1} min^{-1}	No. of runs
1 (H)	4.68–51.3	4.6–41.2	934	7
2 (CH_3)	4.37	3.72 ± 0.41	851	4
3 (CH_3O)	4.37	4.12 ± 0.21	945	6
4 (Cl)	4.37	4.28 ± 0.35	980	5

droxide ion catalysis was therefore ignored in the data when amine catalysts were used, and any error in this approximation is slight and does not affect mechanistic conclusions.

Rate constants for elimination reactions of 4-(*p*-anisoxy)-2-oxobutanoic acid (3) in dimethylaminoethanol buffers were obtained at five pH values. At pH values below the pK_a (9.45), plots of k_{obsd} vs. $[B]_t$ were typically biphasic with a positive final slope. However, when pH exceeded pK_a, the final slopes of the plots were $\simeq 0$, as determined by computer fit of the data to the NLIN program, and the data therefore fit eq 2. At the two higher pH values, the Eadie–Hofstee type plots were found to be linear (Figure 5), as required by the fit of the data to eq 2.

Rate constants were obtained for reactions of 4-(*p*-chlorophenoxy)-2-oxobutanoic acid (4) with morpholine in D_2O at pD 9.01. The reactions generally gave good linear pseudo-first-order plots at very low concentrations of amine (0.01–0.02 M), but at higher amine concentrations the initial slope changed to a smaller final slope (plots not shown). Similar biphasic plots have been observed with other elimination reactions when D_2O is the solvent.[4,6] The curved plots can be explained by assuming rapid, reversible formation of a carbanion intermediate, followed by slower decomposition of the intermediate to products. For such a reaction, α-hydrogen exchange would be faster than elimination, so that at the beginning of the reaction only α,α-diprotio substrate is present, but as the reaction proceeds the concentration of the α-deuterio substrate builds until, toward the end of the reaction, only α,α-dideuterio substrate is the reactant. The curvature in the first-order plot is the result of faster elimination from the more acidic α,α-diprotio substrate than from the α,α-dideuterio substrate in D_2O; the rate of product formation thus decreases as the reaction progresses. At low concentrations of general base, as stated above, $k_{\text{obsd}} = k_1 f r_B [B]_t$ and carbanion formation is rate determining (Scheme I), so that in this case α-hydrogen exchange would not be observed and first-order plots would be linear, as was observed. The shapes of the pseudo-first-order plots offered strong qualitative evidence for the formation of a carbanion intermediate and for an E1cB mechanism. Quantitative data that was obtained was also in agreement with an E1cB mechanism. The k_{obsd} value obtained at $[B]_t = 0.01$ M was 0.0677 min^{-1} ($fr_B[B]_t = 0.00409$ M).[31] The k_{obsd} value calculated from the data of Table I for the reaction of 4 with morpholine in water was 0.0652 min^{-1} ($fr_B[B]_t = 0.00409$ M). At this low $[B]_t$ value, the deuterium solvent isotope effect reflects α-proton abstraction and $k(D_2O)/k(H_2O) = 1.04$, close to the value of 1.07 found by More O'Farrell and Slae[4] for α-proton abstraction in the elimination of methanol from 9-fluorenylmethanol.

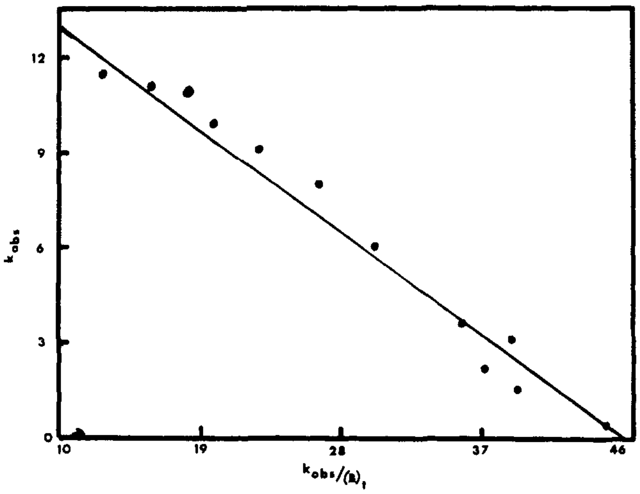


Figure 5. Eadie–Hofstee type plot of the pseudo-first-order rate constant, k_{obsd}, vs. $k_{\text{obsd}}/[\text{dimethylaminoethanol}]_{\text{total}}$ for reactions of 4-*p*-anisoxy-2-oxobutanoic acid (3) with that amine at pH 9.76.

Table III. Deuterium Solvent Kinetic Isotope Effects for Reactions of 4 with Morpholine[a]

$[\text{Morpholine}]_t$, M	k_{obsd}, min^{-1} (D_2O)	k_{obsd}, min^{-1} (H_2O)[b]	$k_{\text{obsd}}(D_2O)/k_{\text{obsd}}(H_2O)$
0.08	0.655	0.429	1.53
0.1	0.743	0.514	1.45
0.2	1.12	0.866	1.30
0.3	1.32	1.15	1.15
0.4	1.90	1.41	1.35
0.5	2.92	1.64	1.78
0.6	3.30	1.87	1.77
0.7	5.40	2.08	2.60
0.8	6.23	2.29	2.72
0.9	6.32	2.50	2.53
1.0	6.36	2.70	2.35

[a] pD 9.01 was obtained by adding 0.4 to the pH meter reading at 30 °C. [b] Calculated for morpholine-catalyzed reactions at pH 8.46.

When the pseudo-first-order plots were curved, at high $[B]_t$, the final limiting slopes of the plots were taken to represent the elimination from α,α-dideuterio substrate in D_2O. The rate constants were estimated by graphical determination of the limiting straight lines at long periods of time from plots of ln ($OD_\infty - OD_t$) vs. time. The deuterium solvent isotope effect was calculated using the calculated k_{obsd} values for elimination from α,α-diprotio-4 in H_2O at pH 8.46 using morpholine as the base (same concentration of the base form of morpholine for each rate constant comparison), so that the estimated isotope effect represents the ratio of elimination of α,α-dideuterio-4 in D_2O to α,α-diprotio-4 in H_2O. The

Table IV. Rate Constants and Rate Constant Ratios for Reactions of 1–4 with Amines According to Equation 7[a]

Compd	Amine	k_1, M^{-1} min^{-1}	k_2/k_3, M^{-1}	k_3^A/k_3, M^{-1}
1 (H)	Morpholine	15.9	13.8	1.30
2 (CH_3)	Morpholine	16.2	21.1	1.78
3 (CH_3O)	Morpholine	12.5	8.47	0.489
4 (Cl)	Morpholine	16.5	6.25	2.34
1 (H)	Imidazole	0.482	12.6	0.945
3 (CH_3O)	Imidazole	0.301	8.72	0.608
1 (H)	Diethanolamine	9.79	10.3	3.43
3 (CH_3O)	Dimethylaminoethanol	62.9	7.17	0.548

[a] Average of five values, except for the reactions of **3** with imidazole (1 value) and with dimethylaminoethanol (5 values of k_1 and 3 values of k_2/k_3 and k_3^A/k_3) (pH 8.8, 9.12, and 9.38).

Scheme II

$$1\text{–}4 \underset{k_2,\ BH}{\overset{k_1,\ B}{\rightleftharpoons}} (1\text{–}4)^- \xrightarrow{k_3,\ k_3^A,\ BH} \text{products}$$

isotope effects obtained in this manner are approximate since there is no way of telling if the limiting condition of complete exchange was ever reached. These data are listed in Table III. The data show that at most concentrations of morpholine the solvent isotope effect was approximately 1.4–1.7, although the values were higher at higher $[B]_t$. Taken as a group, these isotope effects are closer to those reported for E1cB mechanisms than for concerted E2 processes; E1cB-type elimination of methanol from β-methoxy ketones from β-phenoxyethyldimethylsulfonium iodide gave solvent isotope effect values of 1.15–1.3[32] and 1.52,[33] respectively, and E2-type elimination should give a solvent isotope effect of less than 0.5.[1,4,32]

Discussion

The kinetics results obtained for the general-base-catalyzed elimination of para-substituted phenols from 1–4 indicate the operation of a E1cB mechanism. The curvilinear k_{obsd} vs. $[B]_t$ plots (Figure 1) are strong evidence for an intermediate in this reaction, and the carbanionic nature of that intermediate is supported by the deuterium solvent isotope data. The curvilinear plots for the reactions of 4 with morpholine in D_2O strongly indicate that α-hydrogen exchange is faster than elimination at high base concentrations, and the magnitude of the isotope effects is consistent with an E1cB mechanism. A possible mechanism for this reaction is outlined in Scheme II, which is a variant of the simple E1cB mechanism of Scheme I.

In order to accommodate the final nonzero slope (Figure 1, Table I), a general-acid-catalyzed pathway for carbanion decomposition is postulated to occur simultaneously with the uncatalyzed pathway to products. The steady-state equation for Scheme II is eq 7. At the limits of low and high amine concentration, the equation reduces to two linear equations, eq 6 at low amine concentrations and eq 8 at high amine concentrations. The constant k_1 and the rate constant ratios k_2/k_3 and k_3^A/k_3 were calculated from eq 6, 7 and 8 and the data of Table I and are provided in Table IV. Hammett ρ' values, obtained for the reactions of 1–4 with morpholine, may be computed from these data, and we have used ρ' as a guide to the reaction mechanism.[34]

$$k_{obsd} = (k_1[B] + (k_1k_3^A/k_3)[B][BH])/(k_2/k_3 + k_3^A/k_3)[BH] + 1) \quad (7)$$

$$k_{obsd}\,(\text{final}) = (k_1k_3^A/(k_2 + k_3^A)[B] + (k_1k_3K_a/(k_2 + k_3^A)K_w)a_{OH}) \quad (8)$$

The dependence of k_1 and k_2/k_3 on electronic effects of para substituents in 1–4 is also consistent with the E1cB mechanism of Scheme II. The rate constant k_1 is quite insensitive to electronic effects of para substituents (ρ' 0.085), as anticipated for carbanion formation at a site remote from the substituents. As for k_2/k_3, it would be anticipated that the ratio would decrease with increasing σ' value; the rate of protonation of carbanions $(1\text{–}4)^-$ to re-form 1–4 should decrease slightly while k_3 should increase appreciably with an increase in σ'. Indeed, the predicted decrease in k_2/k_3 was observed (ρ' −0.8). The mechanism of Scheme II also features general acid catalysis for the breakdown of carbanion to products, as was proposed for the dehydration of 9-hydroxy-10-methyl-2-*cis*-decalone.[6] However, such catalysis should be much less important for 1–4 than for the 2-decalone because phenols–phenoxide ions are much better leaving groups than water–hydroxide ions. For elimination from 4-(para-substituted-phenoxy)-2-butanones,[5] there is no evidence to support the existence of a general acid pathway from carbanions to products, and based on the concept[35] that general acid–base catalysis will occur where most needed and in a manner such that unstable species are not produced, general acid catalysis for the breakdown of 1–4 carbanions would not be expected. Also, experimental evidence disfavors this feature of mechanism. The ratio k_3^A/k_3 (Table IV) should decrease with an increase in the electron-withdrawing power of para substituents. However, the ratio increases (ρ' 0.5). These considerations suggest that an alternative mechanism for the reactions of 1–4 would be more appropriate.

Scheme III (not shown) is Scheme I with an additional pathway from 1–4 to products, which is a concerted general-base-catalyzed pathway ($k_4[B]$). Scheme III gives a steady-state equation which has the same form as eq 4, namely eq 9. The scheme involves the simultaneous occurrence of E1cB- and E2-type reactions as proposed by More O'Farrell[36] for the elimination of methanol from 9-fluorenylmethanol. On theoretical grounds and on the basis of the deuterium solvent isotope effect results, we disfavor the mechanism of Scheme III. As Jencks[37] has pointed out, the primary reason for a concerted mechanism such as an E2 mechanism lies in the avoidance of highly unstable intermediates that would be required for a stepwise mechanism. If such an unstable intermediate were present in the elimination of 1–4 it would be much more likely to decompose than to exchange an α-hydrogen for deuterium. The results of this study indicate that exchange can be faster than elimination. Also, we call attention to the result that at pH 9.76 and 10.02 elimination from 2 catalyzed by dimethylaminoethanol can be adequately described by the mechanism of Scheme I. This is equivalent to saying that there is a loss of the E2 pathway as the pH is raised within the same buffer series, and there is no reason why this should happen. However, to the extent that the experimental result may be artifactual (vide infra), this argument against Scheme III is less compelling.

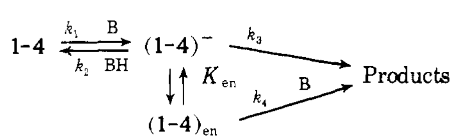
$$k_{obsd} = ((k_1 + k_4)[B] + (k_2k_4/k_3)[B][BH])/((k_2/k_3)[BH] + 1) \quad (9)$$

An alternative mechanism which we favor is that of Scheme IV which features a rapid equilibrium between carbanions and

Table V. Calculated Rate Constants for the Mechanism of Scheme IV

Compd	pK_{SH}	k_2, M^{-1} min^{-1}	k_3, min^{-1}	k_4/K_{en}, min^{-1}	σ'
1 (H)	13.20	6.11×10^5	4.42×10^4	2.39×10^{13}	0
2 (CH_3)	13.21	6.30×10^5	2.98×10^4	2.21×10^{13}	−0.16
3 (CH_3O)	13.25	5.37×10^5	6.34×10^4	1.29×10^{13}	−0.23
4 (Cl)	13.09	4.93×10^5	7.88×10^4	7.68×10^{13}	0.6

Scheme IV



enols, as postulated by Hupe et al.[6] for the dehydration of 9-hydroxy-10-methyl-2-*cis*-decalone; spontaneous decomposition of carbanions and general-base-catalyzed decomposition of enols gives products. The steady-state equation for Scheme IV is given by eq 10. In eq 10, the initial slope is still k_1 (Table IV), the ratio k_2/k_3 is the same as that calculated from eq 9 of Scheme III (Table IV), and the ratio k_4K_a/K_{en} is mathematically equivalent to the rate constant $k_3{}^A$ of Scheme III. However, in contrast to the predicted dependence of the ratio $k_3{}^A/k_3$ in Scheme III on the Hammett σ' values, the ratio k_4K_a/k_3K_{en} of Scheme IV should increase with an increase in the electron-withdrawing properties of para substituents, as is the case. We computed ρ' values for k_2, k_3, and k_4/K_{en} based on the calculated values of these constants. Although the computed values are likely incorrect because they are based on the ionization constants (K_{SH}) of **1–4**, which must be estimated, their relative values are likely correct since they are based on experimental values, and the ρ' values should be correct as well. From the relationship $k_1/k_2 = K_{SH}/K_a$,[6] the assumption that K_{SH} (1-4)/K_{SH} (4-aryloxy-2-butanones) = K_{SH}(pyruvic acid)/K_{SH}(acetone) = $k_{enolization}$(pyruvic acid)/$k_{enolization}$(acetone), and the data of Table IV, the necessary constants may be calculated. Schellenberger and Hubner[38] have measured the ratio of rate constants for the general-base-catalyzed enolization of pyruvate and acetone; its value is 17.5. The values of K_{SH} for **1–4** were therefore assumed to be 17.5 times greater than those estimated for 4-aryloxy-2-butanones.[6] Table V gives the values of the constants from which ρ' (k_2) = −0.09, ρ' (k_3) = 0.3, and ρ' (k_4/K_{en}) = 0.8 may be computed.

Although the correlation coefficients of the regressions are not very good (r = 0.62–0.98), the resultant ρ' appear to be reasonable for the mechanism of Scheme IV. We assume that $\rho'(k_4/K_{en})$ essentially reflects electronic effects on the k_4 step. An interesting aspect of this exercise is the result that elimination from enols via k_4 is more sensitive to electronic effects than is elimination from enolates via k_3. This would be true if the extent of C–O bond breaking in the transition state for elimination from enols was greater than that for elimination from enolates. Noting that **1–4** exist as carboxylate anions in morpholine buffer solutions, we believe that the enolate dianion would be a high-energy intermediate, and elimination from it would involve an early transition state. On the other hand, the enol could be well stabilized via ion-reinforced hydrogen bonding, and elimination from it could well involve a later transition state. Here it is well to point out that elimination from enols of 4-aryloxy-2-butanones appears not to be kinetically important, which may reflect the lessened stability of these enols relative to those of **1–4**. Also, ρ' (k_3) for 4-aryloxy-2-butanones should be greater than ρ' (k_3) for **1–4**, and this is the case.

$$k_{obsd} = (k_1[B] + (k_1k_4K_a/k_3K_{en})[B][BH])/((k_2/k_3 + k_4K_a/k_3K_{en})[BH] + 1) \quad (10)$$

Further support for the mechanism of Scheme IV may be found in a literature analogy for general base catalysis of proton transfer from enol OH. Hegarty and Jencks[39] recently examined the product term, k_{AB}[acid][base], for the enolization of acetone, and they concluded that the most likely involvement of the acid–base pair is in concerted proton transfer. The reverse ketonization reaction then involves concerted proton transfer from enol OH to a general base and from general acid to an enolic carbon. If this conclusion is correct, then postulated enols of this study could well employ general base catalysis of proton transfer from enol OH and achieve a stable configuration (products) by transferring electrons to the leaving aryloxide ion rather than to a general acid. On theoretical grounds, the incursion of general base catalysis in the k_4 step could be predictable on the basis that conversion of the enol to products involves a pK change of greater than 15, with formation of the unstable keto-protonated 2-oxobutenoic acid; proton transfer during elimination would avoid formation of this unstable product.[37,40]

For reactions of **3** in dimethylaminoethanol, the change in the limiting slope at high amine concentrations to approximately 0 (Table I) at pH 9.76 and 10.02 remains questionable; in terms of the mechanism of Scheme IV, it is as if the k_4 step has diminished to the point of undetectibility. We attempted to address the question by examining the consistency of the data by computing various rate constants or rate constant ratios of equation 10 using that equation, eq 4, and the data of Table I. For the five pH values, $k_1 = 62.9 \pm 5.1$ M^{-1} min^{-1}. For pH 8.81, 9.12, and 9.38, k_2/k_3 = 6.64, 7.39, and 7.78 M^{-1}, and the value of k_4K_a/k_3K_{en} is ~7% of the term ($k_2/k_3 + k_4K_a/k_3K_{en}$). If the k_4-containing term is ignored and k_2/k_3 is calculated for pH 9.76 and 10.02, the values are 7.66 and 9.13 M^{-1}, not significantly different from those values obtained for lower pH's. All five values of the set give $k_2/k_3 = 7.68 \pm 0.97$ M^{-1}. The k_1 and k_2/k_3 values may be compared with those of 4-anisyloxy-2-butanone, which are 5.49 M^{-1} min^{-1} and 7.8 M^{-1} min^{-1}, respectively.[6] The data thus seem to be consistent, and we may conclude that the apparent loss of the k_4 term is the result of general-base-catalyzed conversion of enol to products becoming noncompetitive with spontaneous conversion of enolate to product as pH is raised. At high concentrations of dimethylaminoethanol buffer (~1 M), the $q[B]_t{}^2$ term constitutes ~30 (pH 8.81) to 10% (pH 10.02) of the numerator term of eq 4; the k_4K_a/k_3K_{en} part of the $r[B]_t$ term remains at ~7% of this denominator term over the pH range of the experiments. Arithmetically, the k_4-containing terms become increasingly difficult to detect as pH increases.

It appears to us that, of the three possible schemes presented, Scheme IV is the most reasonable on experimental and theoretical grounds. For the mechanism of Scheme IV, the general-acid-catalyzed formation of enol directly from **1** to **4** might be expected, since this is a known reaction.[35] However, the plots of $k_{obsd}/[B]_t$ vs. fr_B (Figure 3) imply that the formation of an intermediate (s) is not general acid catalyzed to any great extent. In this regard, previous studies of the enolization of α-keto acids have shown that enolization is predominantly general base catalyzed; both Schellenberger and Hübner[38] and Hegazi and Meany[41] found that enolization of pyruvic acid is not acid catalyzed to any great extent. Analogously, general acid catalysis for enolization of **1–4** would not necessarily be expected, and the mechanism of Scheme IV remains reasonable.[45]

Finally it is interesting to speculate on the reason why **1–4** undergo elimination by a mechanism that is more complex than the mechanism of elimination of 4-aryloxy-2-butanones (Scheme I).[6,43] It might be reasonable for **1–4** to undergo elimination via an enol intermediate, while the corresponding ketones would not undergo such an elimination if the enol form of **1–4** would be more stable relative to the keto form than would the enol form of 4-aryloxy-2-butanones. A more stable tautomer would mean that it would be more energetically favorable for enolate anions to react to form enol rather than collapse back to keto tautomers in the initial steps before product is formed. A quantitative measure of the relative stabilities of the various tautomers is the keto–enol tautomerism equilibrium constant. The constants have not been measured for **1–4** or for the corresponding 4-aryloxy-2-butanones, but equilibrium constants for analogous compounds can give some insight into the stability of the enols. The equilibrium constant for enolization of acetone, calculated from the data of Schwarzenbach and Wittwer,[42] is 2.5×10^{-6}. From the data of Schellenberger and Hübner,[38] the equilibrium constant for enolization of 2-oxobutanoic acid is 6.6×10^{-3}. The 10^3 difference in equilibrium constants is a significant indicator that formation of enol from enolate would be more likely for **1–4** than for 4-aryloxy-2-butanones.

Acknowledgment. We wish to thank Mr. William Hendricks for his assistance in obtaining the primary kinetic data. This work was supported in part by a grant from the U.S. Public Health Service.

Registry No.—Benzyl diethoxyacetate, 64114-01-8; diethoxyacetic acid, 20461-86-3; benzyl chloride, 100-44-7; 2-carbobenzoxy-1,3-dithiane, 64114-00-7; 1,3-propanedithiol, 109-80-8; *p*-bromophenetole, 589-10-6; *p*-methyl-β-bromophenetole, 18800-34-5; *p*-methoxy-β-bromophenetole, 22921-76-2; *p*-chloro-β-bromophenetole, 2033-76-3; 2-(β-phenoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-99-1; 2-(β-*p*-cresoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-98-0 2-(β-*p*-anisoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-97-9; 2-(β-*p*-chlorophenoxy)ethyl-2-carbobenzoxy-1,3-dithiane, 64113-95-7; benzyl 4-phenoxy-2-oxo-butanoate, 64113-96-8; benzyl 4-(*p*-cresoxy)-2-oxobutanoate, 64113-94-6; benzyl 4-(*p*-anisoxy)-2-oxobutanoate, 64113-93-5; benzyl 4-(*p*-chlorophenoxy)-2-oxobutanoate, 64113-92-4.

References and Notes

(1) W. H. Saunders and A. F. Cockerill, "Elimination Reactions", Wiley-Interscience New York, N.Y., 1973.
(2) L. R. Fedor, *J Am. Chem. Soc.*, **91,** 913 (1969).
(3) R. C. Cavestri and L. R. Fedor, *J. Am. Chem. Soc.*, **92,** 4610 (1970).
(4) R. A. More O'Farrell and S. Slae, *J. Chem. Soc. B*, 260 (1970).
(5) L. R. Fedor and W. R. Glave, *J. Am. Chem. Soc.*, **93,** 985 (1971).
(6) D. J. Hupe, M. C. R. Kendall, G. T. Sinner, and T. A. Spencer, *J. Am. Chem. Soc.*, **95,** 2260 (1973).
(7) H. P. Meloche and J. P. Glusker, *Science*, **181,** 350 (1973).
(8) B. F. Tack, P. J. Chapman, and S. Dagley, *J. Biol. Chem.*, **246,** 6444 (1972).
(9) H. Nishihara and E. E. Dekker, *J. Biol. Chem.*, **247,** 5079 (1972).
(10) G. W. Kosicki and F. W. Westheimer, *Biochemistry*, **7,** 4303 (1968).
(11) D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *J. Biol. Chem.*, **247,** 2751 (1972).
(12) R. Jeffcoat, H. Hassall, and S. Dagley, *Biochem. J.*, 977 (1968).
(13) K. Bloch, *Enzymes, 3rd Ed.*, **5,** 441 (1971).
(14) R. R. Rando, *Science*, **185,** 320 (1974).
(15) R. R. Rando, *Biochem. Pharmacol.*, **24,** 1153 (1975).
(16) R. H. Abeles and A. L. Maycock, *Acc. Chem. Res.*, **9,** 313 (1976).
(17) K. Samochoka and J. Kowalczyk, *Radiochem. Radioanal. Lett.*, **4,** 131 (1970).
(18) L. Lang, Ed., "Absorption Spectra in the Ultraviolet and Visible Region", Vol. 2, Academic Press, New York, N.Y., 1961, p 144.
(19) R. B. Moffett, "Organic Synthesis", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 427.
(20) E. J. Eliel and A. A. Hartman, *J. Org. Chem.*, **37,** 505 (1972).
(21) R. Adams and A. F. Thal, "Organic Synthesis", Collect. Vol. I, Wiley, New York, N.Y., 1956, p 436.
(22) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36,** 3553 (1971).
(23) For a listing of pseudo-first-order rate constants see J. M. Hilbert, Ph.D. Thesis, State University of New York at Buffalo, 1976.
(24) E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **84,** 3505 (1962).
(25) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **86,** 5616 (1964).
(26) T. C. Bruice and L. R. Fedor, *J. Am. Chem. Soc.*, **86,** 4886 (1964).
(27) W. P. Jencks and K. Salversen, *J. Am. Chem. Soc.*, **93,** 1419 (1971).
(28) R. Hirschfield and G. L. Schmir, *J. Am. Chem. Soc.*, **95,** 8032 (1973).
(29) R. M. Pollack and T. C. Dumsha, *J. Am. Chem. Soc.*, **97,** 377 (1975).
(30) The Eadie–Hofstee equation was used in preference to the more commonly used Lineweaver–Burke equation because the Eadie–Hofstee plot was found to give a better statistical weighting of the points; J. E. Dowd and D. S. Riggs, *J. Biol. Chem.*, **240,** 863 (1965).
(31) The pK (D_2O) of morpholine, determined by the method of fractional neutralization, is 9.17 (30 °C) and the pK (H_2O) of morpholine is 8.62.
(32) L. R. Fedor, *J. Am. Chem. Soc.*, **89,** 908 (1967).
(33) J. Crosby and C. J. M. Stirling, *J. Chem. Soc. B*, 679 (1970).
(34) σ' values were computed from the ionization constants of para-substituted phenols and were used to obtain ρ' values; A. Albert and E. P. Seargent, "Ionization Constants of Acids and Bases", Wiley, New York, N.Y., 1962, p 130.
(35) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, Chapter 3.
(36) R. A. More O'Farrell, *J. Chem. Soc. B*, 274 (1970).
(37) W. P. Jencks, *Chem. Rev.*, **72,** 705 (1972).
(38) A. Schellenberger and G. Hübner, *Chem. Ber.*, **98,** 1938 (1965).
(39) A. F. Hegarty and W. P. Jencks, *J. Am. Chem. Soc.*, **97,** 7188 (1975).
(40) W. P. Jencks, *Acc. Chem. Res.*, **9,** 425 (1976).
(41) M. Hegazi and J. E. Meany, *J. Phys. Chem.*, **76,** 3121 (1972).
(42) H. G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30,** 669 (1947).
(43) In a previous study, where rate saturation kinetics were reported for the elimination reactions of 4-aryloxy-2-butanones in aqueous dimethylaminoethanol (DMAE), amine concentrations generally did not exceed 0.2 M, so that the question of saturation may not have been adequately addressed. In subsequent work (L.F.), saturation kinetics were reexamined in aqueous dimethylaminoethanol (0.15–3.0 M, $fr_B = 0.67$, ionic strength 1.0 M (KCl)), and the following results were obtained ($k_{obsd} - k_{OH}a_{OH}$ (min^{-1}), $[DMAE]_t$ (M)): 0.346, 0.15; 0.554, 0.3; 0.804, 0.6; 0.965, 0.9; 1.044, 1.2; 1.076, 1.5; 1.078, 1.8; 1.115, 2.1; 1.078, 2.4; 1.105, 2.7; 1.030, 3.0. From these data, k_1 (Scheme I) = 4.7 M^{-1} min^{-1} and k_2/k_3 (Scheme I) = 5.96 M^{-1}, which both compare well with the reported values of 4.44 ± 0.44 M^{-1} min^{-1} and 6.45 ± 1.97 M^{-1} for reactions of 4-phenoxy-2-butanone with dimethylaminoethanol.
(44) We examined some solvent and salt effects to test if the nonzero final slopes (Figure 1) are due to such effects. For reactions of 4-*p*-cresoxy-2-oxobutanoic acid (**2**) in 0.05 M morpholine buffer, pH 8.13, the k_{obsd} (min^{-1}) and total salt, morpholine hydrochloride and potassium chloride, concentrations (M) are as follows: 0.130, 0.1; 0.121, 0.2; 0.121, 0.3; 0.127, 0.5; 0.139, 0.7; 0.127, 0.9. Thus, k_{obsd} is little affected by changes in KCl concentration in the range 0.1–0.9 M. Replacement of KCl with tetramethylammonium chloride (TMAC) slightly decreased k_{obsd} for elimination in 0.05 M morpholine, pH 8.22, μ 1.0 M (KCl + TMAC). k_{obsd}, [TMAC] are: 0.123, 0; 0.121, 0.1; 0.115, 0.2; 0.109, 0.4; 0.101, 0.6; 0.101, 0.8. The use of 1,4-dioxane as a cosolvent had either no effect on k_{obsd} or else caused a decrease in its value. For reactions of **2** with 0.05 M morpholine in aqueous dioxane, pH 8.16 and μ 1 M (KCl), k_{obsd} (min^{-1}) and dioxane concentrations (M) are as follows: 0.121, 0; 0.119, 0.1; 0.111, 0.2; 0.103, 0.4; 0.109, 0.6; 0.130, 0.8. For 0.25 M morpholine, pH 8.16, the values are as shown: 0.313, 0; 0.330, 0.1; 0.280, 0.2; 0.285, 0.3; 0.272, 0.4; 0.253, 0.5. For 1 M morpholine, pH 8.90, the values are the following: 2.22, 0; 1.92, 0.2; 1.73, 0.4; 1.64, 0.6; 1.49, 0.8; 1.39, 1.0. For 0.2 M morpholine, pH 8.90, the values are as follows: 1.08, 0; 1.01, 0.2; 0.979, 0.4; 0.829, 0.8; 0.748, 1.2; 0.576, 1.6.
(45) We believe that elimination from **1–4** via imminium ions may play at most a very minor role in the chemistry of this study: (1) No intermediates were detected spectroscopically using **1** in morpholine buffers. (2) Rate constants have values in accord with predictions based on the results of elimination from 4-(para-substituted-phenoxy)-2-butanones.[5] (3) The kinetics of elimination of phenol from **1** catalyzed by *N*-ethylmorpholine are similar to those of this study. Data were not reported for the runs done at two pH values because amine solutions became yellow on standing. (4) The kinetics of elimination from **1** catalyzed by trifluoroethylamine (J.M.H., Ph.D. Thesis) are different from those reported here, and they resemble those reported by Hupe et al.[46,47] for covalent catalysis of elimination from 9-acetoxy-10-methyl-*cis*-decal-2-one. (5) The kinetics of elimination from **1** catalyzed by ethanolamine (J.M.H., Ph.D. Thesis) resemble those of **1–4** of this study, but the pH dependence of the rate constants is not that predicted by eq 10; e.g., k_1 has an apparent acidity dependence. In regard to this last point, isomerization of 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one to the conjugated steroid is markedly catalyzed by aminoethanol while it is sluggishly transformed by tertiary amine, and the kinetics of the aminoethanol reaction resemble those of **1** in aminoethanol buffer solutions (S. Perera and L. Fedor, unpublished results).
(46) D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Am. Chem. Soc.*, **94,** 1254 (1972).
(47) D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Am. Chem. Soc.*, **95,** 2271 (1973).