Solvolysis in Dipolar Aprotic Solvents. Behavior of 4-(*p*-Substituted phenyl)-4-oxo-2-bromobutanoic Acids in Dimethyl Sulfoxide. Substituent Effect[1]

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A kinetic study of the substituent effect on the reactivity of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids in the solvolytic elimination in Me_2SO was carried out. It was found that electron-withdrawing groups increased the rate of reaction and electron-donating groups decreased the rate. Hammett correlation of this substituent effect was obtained with σ values in Me_2SO-d_6 at 36 and 60 °C. The ρ observed value, the isotopic effect, and the leaving group influence support a mechanism in which the proton is lost in the rate-determining step of reaction.

Recent studies on solvolysis in dipolar aprotic media[2] have recorded the interesting behavior of Me_2SO as solvent for reaction with alkyl halides and related compounds.[3]

The present paper describes our kinetic studies by means of NMR spectroscopy on the solvolytic elimination in Me_2SO-d_6 of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids (**1**).[4]

The 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids in Me_2SO-d_6 yielded quantitatively the corresponding trans olefines (**2**).[5] The concentration of reactants, at any given time, during the solvolysis was determined by NMR spectroscopy. The rate of reaction[6] was usually followed by observing the distinct integration area of each peak: disappearing peak of methine proton, appearing peaks of olefinic protons. It was found that a plot of log $[\text{butanoic acid}]_{t=0}/[\text{butanoic acid}]_t$ vs. time, for all acids used, yielded a straight line. The rate constant was determined from the slope of the straight line at 36 and 50 °C. The linear observed relation indicates a first-order reaction (Table I).

$$RC_6H_4COCH_2CHBrCOOH \xrightarrow{Me_2SO} RC_6H_4COCH{=}CHCOOH$$

1a, R = H
b, R = F
c, R = Cl
d, R = Br
e, R = NO_2
f, R = CH_3
g, R = OCH_3

2a, R = H
b, R = F
c, R = Cl
d, R = Br
e, R = NO_2
f, R = CH_3
g, R = OCH_3

The presence of a carbonyl group introduces the possibility of an HBr catalytic step, but we cannot suggest anything which would give rise to the kinetic and to the observed products.

Hammett Relationship

Kinetic studies of substituent effect on the rate of reaction of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids in Me_2SO-d_6 showed that electron-withdrawing groups increased the rate of reaction and electron-donating groups decreased the rate of reaction (Table I), although the substituent is removed from direct conjugation in the system for a carbonyl group. The Hammett relationship was obtained from the kinetic constant of reactions, using σ values. The ρ values at 36 and 50 °C support a transition state with small anionic character[7] (Table II).

Results and Discussion

In order to investigate the factors influencing the electronic state of two reaction sites, in relation to the high nucleophilicity and basicity of Me_2SO,[8] we have examined the behavior in Me_2SO of some correlated systems.

We have then noted the inductive influence of a substituent on the sites of reaction by comparison of the solvolytic constant in Me_2SO of 4-oxo-2-bromopentanoic acid[9] with the constants of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids. These kinetic values are similar to the K_a of acetic acid and *p*-substituted phenylacetic acids (Table I).[10]

On the other hand, we have observed that 4-(*p*-substituted phenyl)-4-oxo-3-bromobutanoic acids (**3**) are unable to decompose to olefins, by elimination, in Me_2SO. It is noteworthy that instead of olefins, after some days, from the mixture of reaction, 4-(*p*-substituted phenyl)-4-oxo-3-hydroxybutanoic acids[11] were recovered (yield 60%), consequent to the nucleophilic attack of Me_2SO on the C_3 of 4-(*p*-substituted phenyl)-4-oxo-3-bromobutanoic acids, this C_3 being electron poor in the presence of a more electron-withdrawing neighbor.

Moreover, in the solvolytic reaction in Me_2SO of the 2-bromosuccinic acid,[12] elimination and substitution are competitive, and fumaric and malic acids (10:90) are formed, according to the electronic state of the substrate.

On the contrary, the reaction of dibenzoylbromoethane in Me_2SO yielded some of dibenzoylhydroxyethane and almost quantitatively dibenzoylethylene.[13]

The anionic character of the transition state observed in the solvolytic elimination of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids in Me_2SO-d_6 by the Hammett relationship justified a more probing investigation.

The isotopic effect carried out on the solvolysis of 4-phenyl-4-oxo-2-bromobutanoic-*3*-d_2 acid in Me_2SO-d_6 yielded K_H/K_D = 2.1. This value[14] seems to be further proof for the transfer of a hydrogen in the rate-determining step of reaction, according to the just-reported substituent effect.

No deuterium exchange was observed during solvolytic elimination on the unreacted substrates in Me_2SO-d_6, CD_3OD, nor $CDCl_3$. No measurable deuterium exchange was detected by addition of DCl[15] to the reaction mixture.

Significantly, no valuable keto–enolic equilibrium was affected or induced. Moreover, we have examined the behavior to the solvolysis in Me_2SO-d_6 of the 4-phenyl-4-oxo-2-chlorobutanoic acid[16] in order to note the influence on the rate of reaction of the leaving group with regard to the 4-phenyl-4-oxo-2-bromobutanoic acid. The presence of Cl as a leaving group makes the reaction (ca. three times) slower according to Br > Cl as the leaving group. It is noteworthy that the solvolysis of 4-phenyl-4-oxo-2-chlorobutanoic acid which is initially slow increases to a maximum for the developing HCl (critical value of HCl concentration is ~1%), and this behavior is usually indicative of autocatalysis. The great activity of Cl^-

Table I. Rate Constants for the Solvolytic Reaction in Me_2SO of 4-(*p*-Substituted phenyl)-4-oxo-2-bromobutanoic Acids and 4-Oxo-2-bromopentanoic Acid at 36 and 50 °C

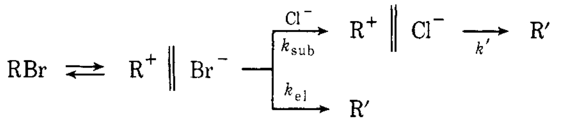
Substituent	Rate constant, M^{-1} min^{-1}, $10^4 k$ 36 °C	50 °C
p-CH_3	8.0	19.3
p-OCH_3	6.0	14.4
H	9.0	22.0
p-F	9.8	24.8
p-Cl	13.1	33.1
p-Br	14.5	36.0
p-NO_2	30.3	78.2
4-Oxo-2-bromopentanoic acid	6.4	16.1

in Me_2SO is well known and on this subject we record the small tendency of Me_2SO to solvate anions.[17]

We have then examined the solvolysis in Me_2SO-d_6 of 4-phenyl-2-bromo-4-oxobutanoic acid when an equimolecolar quantity of LiBr and LiCl was added to the reaction mixture. It is unambiguous that Br^- was substituted rapidly by Cl^- (5′) in the solvent-separated ion pair; subsequently the elimination begins on the 4-phenyl-4-oxo-2-chlorobutanoic acid.

On the contrary, only a common salt effect for the LiBr was observed.

This result brings to mind that the ion pair is so large a solvent separated one as to allow a substitution reaction and $K_{sub} \gg K_{el}$ (R′ = olefin).



Owing to the experimental results on the solvolysis of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids in Me_2SO-d_6, E1 and E1cb mechanisms as extremes of a continuous spectrum of transition states of E2 mechanism are excluded by the observed influence on the rate of reaction of the leaving group, substituent effect, isotopic effect, and negative results of deuterium exchange although the last criterion[15] is often ambiguous for its dependence on reprotonation kinetics, proton mobility in the solvent, and acid catalysis.

An E2 mechanism, in which the Hammett correlation of substituent effect and isotopic effect suggest carbanion character in the transition state, appears to be more reasonable. The small value is probably correlated to the presence of the solvent-separated ion pair that neutralizes the developing charge along the extended bond with considerable ionic character.

We consequently propose for the observed elimination reaction of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acids a transition state in which the solvent-separated ion pair begins to lose the proton developing some negative charge on the C_β. From OCH_3 to NO_2 *p*-substituted phenyl-4-oxo-2-bromobutanoic acids there is a range of spectrum of transition state in which the charge present on C_β decreased for the inductive influence of *p*-substituent.

Experimental Section

All kinetic measurements were made on a Perkin-Elmer R-24 instrument. The accuracy of the NMR integration was ±5.0%. IR spectra were obtained on a Perkin-Elmer 137 E instrument. Weighings were carried out on an analytical balance with an accuracy ±0.0001 g. Dimethyl sulfoxide-d_6 (Merck) was dried on molecular sieves.

Table II. Hammett Relationship of the Solvolytic Reaction in Me_2SO of 4-(*p*-Substituted phenyl)-4-oxo-2-bromobutanoic Acids at 36 and 50 °C

Temp, °C	ρ value	Corr. coeff	s	s_ρ	No. of points
36	0.65	0.99	0.07	0.08	7
50	0.68	0.99	0.04	0.05	7

Kinetic Procedure. A known volume of preheated Me_2SO-d_6 was added to an appropriate amount of 4-(*p*-substituted phenyl)-4-oxo-2-bromobutanoic acid weighed in an NMR tube (4% solution), and a timer was started. The NMR tube was maintained at the probe temperature. The variation found on the probe temperature was less than ±0.3 °C (methanol as standard). The rate of the reaction was determined by integration of the appropriate NMR signals. Five or six integrations were taken at any given time and the average value was used. All the reactions were followed to completion. The reaction is over after ~24 h and the concentration data were recorded every 0.5 h. The method of averages was applied on this set of data for the calculation of the kinetic constants. The reported data of kinetic constants are the average values obtained from ten comparable kinetic runs.

Method of Calculation. It is known that the area of an NMR absorption is proportional to the nuclei contributing to it; thus, the area of the methine peak is proportional to the amount of the butanoic acid present and the area of the olefinic proton is proportional to the amount of the olefin present. Using this rationale the amounts of reactant and product present in the mixture of reaction at any given time were determined as follows. Let M_0 be the initial moles of butanoic acid present and M_t the moles present at any given time t. Let $A_b{}^0$ be the initial area of the methine proton and $A_b{}^t$ the area at any given time t, and let A_P be the area of the olefinic proton at any given time t; then

$$\frac{M_0}{M_t} = \frac{A_b{}^0}{A_b{}^t} = \frac{A_b + A_P}{A_b}$$

The rate constant was determined from the rate equation by plotting $\log (M_0/M_t) = 2.303Kt$.

Formation of 4-(*p*-Substituted phenyl)-4-oxo-2-bromobutanoic acids (1). General Procedure. 3-(*p*-Substituted benzoyl)acrylic acids (2) were prepared by Friedel–Crafts acylations on substituted benzenes with maleic anhydride. To a suspension of these acids in $CHCl_3$ at 0 °C was added gaseous HBr. The solvent was removed by evaporation in vacuo and the precipitate was recrystallized by $CHCl_3$.

1b. Anal. Calcd for $C_{10}H_8BrFO_3$: C, 43.63; H, 2.90. Found: C, 43.80; H, 3.10. IR (KBr) 1690 (C=O), 1720 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.78 (m, 2, CH_2), 4.71 (t, 1, CHBr); mp 108 °C.

1c. Anal. Calcd for $C_{10}H_8BrClO_3$: C, 41.23; H, 2.74. Found: C, 41.30; H, 2.86. IR (KBr) 1688 (C=O), 1735 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.80 (m, 2, CH_2), 4.72 (t, 1, CHBr); mp 120 °C.

1d. Anal. Calcd for $C_{10}H_8Br_2O_3$: C, 50.84; H, 3.38. Found: C, 50.92; H, 3.45. IR (KBr) 1685 (C=O), 1725 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.77 (m, 2, CH_2), 4.68 (t, 1, CHBr); mp 122 °C.

1e. Anal. Calcd for $C_{10}H_8BrNO_5$: C, 39.73; H, 2.64. Found: C, 40.10; H, 2.72. IR (KBr) 1695 (C=O), 1720 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.91 (m, 2, CH_2), 4.75 (t, 1, CHBr); mp 132 °C.

1f. Anal. Calcd for $C_{11}H_{11}BrO_3$: C, 48.70; H, 4.05. Found: C, 48.85; H, 4.11. IR (KBr) 1695 (C=O), 1725 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.75 (m, 2, CH_2), 4.70 (t, 1, CHBr); mp 136 °C.

1g. Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 45.09; H, 3.83. Found: C, 45.21; H, 3.99. IR (KBr) 1675 (C=O), 1710 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.75 (m, 2, CH_2), 4.70 (t, 1, CHBr); mp 127 °C.

3-(*p*-Nitrobenzoyl)acrylic Acid. 4-Nitroacetophenone (0.1 mol) in 7.5 mL of acetic anhydride was added to a homogeneous paste of 0.1 mol of barium glyoxalate in 10 mL of H_2SO_4 concentrated in 20 mL of dried acetic acid. The mixture heated for 2 days at 70 °C was cooled and treated with 200 mL of H_2O. The filtrate from $BaSO_4$ was extracted with $CHCl_3$; the extract, evaporated in vacuo and freed from acetic acid by keeping it over KOH in vacuo, yielded 8.3 g of 3-(*p*-nitrobenzoyl)acrylic acid.

Anal. Calcd for $C_{10}H_7NO_5$: C, 54.30; H, 3.19. Found: C, 54.51; H, 3.25. IR ($CHCl_3$) 1680 (C=O), 1720 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 6.68 (d, 1H), 7.84 (d, 1H), J = 16 Hz; mp 171 °C.

Formation of 4-(*p*-Substituted phenyl)-4-oxo-3-bromobutanoic Acids. General Procedure. Bromine, in small excess, was added dropwise to a solution of 4-(*p*-substituted phenyl)-4-oxo-butanoic acids[16] in $CHCl_3$, at 0 °C. These acids were prepared by Friedel–Crafts acylations on substituted benzenes with succinic anhydride. The mixture refluxed for 2 h was cooled and the solvent was evaporated in vacuo. The precipitate was recrystallized by $CHCl_3$.

***p*-Anisyl-4-oxo-3-bromobutanoic Acid.** Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 45.10; H, 3.83. Found: C, 45.30; H, 3.91. IR (KBr) 1690 (C=O), 1710 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.05 (m, 2, CH_2), 5.70 (dd, 1, CHBr); mp 124 °C.

***p*-Chlorophenyl-4-oxo-3-bromobutanoic Acid.** Anal. Calcd for $C_{10}H_8BrClO_3$: C, 41.23; H, 2.74. Found: C, 41.45; H, 2.83. IR (KBr) 1700 (C=O), 1720 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.18 (m, 2, CH_2), 5.82 (dd, 1, CHBr); mp 118 °C.

***p*-Fluorophenyl-4-oxo-3-bromobutanoic Acid.** Anal. Calcd for $C_{10}H_8BrFO_3$: C, 43.63; H, 2.12. Found: C, 43.70; H, 2.30. IR (KBr) 1700 (C=O), 1725 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.16 (m, 2, CH_2), 5.83 (dd, 1, CHBr); mp 112 °C.

2-Bromolaevulinic Acid. A solution of 4-oxo-2-pentenoic acid in CCl_4 at 0 °C was saturated with gaseous hydrogen bromide. The solvent was evaporated in vacuo at 20 °C and a thick oil was recovered, unstable to heat and water.

Anal. Calcd for $C_5H_7BrO_3$: C, 30.70; H, 3.58. Found: C, 30.83; H, 3.69. IR (KBr) 1710 (C=O), 1725 (COOH) cm^{-1}; NMR ($(CD_3)_2SO$) δ 3.22 (m, 2, CH_2), 4.50 (t, 1, CHBr). Other authors have not succeeded in preparing pure 2-bromolaevulinic acid because of its unstability in aqueous solvents.

***p*-Chlorophenyl-4-oxo-3-hydroxybutanoic Acid.** A solution (4%) of *p*-chlorophenyl-4-oxo-3-bromobutanoic acid in Me_2SO was maintained at room temperature until the product was NMR detectable. The mixture diluted with ether yielded (40%) the initial product, while upon the addition of water *p*-chlorophenyl-4-oxo-3-hydroxybutanoic acid precipitated. The product, isolated and purified by TLC, was identified by mass spectroscopy M^+, 228; NMR ($(CD_3)_2SO$) δ 2.70 (d, 2, CH_2), 5.25 (t, 1, CHOH).

Dibenzoylbromoethane. A solution of dibenzoylethylene in CCl_4 at 0 °C was saturated with gaseous hydrogen bromide. The solvent was evaporated in vacuo and the precipitate was recrystallized by CCl_4 and characterized by mass and NMR spectroscopy. M^+, 317; NMR δ 4 (m, 2, CH_2), 6.0 (dd, 1, CHBr) in ($(CD_3)_2SO$).

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Registry No.—**1a,** 63104-90-5; **1b,** 63104-91-6; **1c,** 63104-92-7; **1d,** 63104-93-8; **1e,** 63104-94-9; **1f,** 63104-95-0; **1g,** 63104-96-1; **2a,** 17812-07-6; **2b,** 35504-85-9; **2c,** 29582-39-6; **2d,** 20972-38-7; **2e,** 63104-97-2; **2f,** 20972-36-5; **2g,** 20972-37-6; 4-nitroacetophenone, 100-19-6; *p*-anisyl-4-oxo-3-bromobutanoic acid, 24849-51-2; *p*-chlorophenyl-4-oxo-3-bromobutanoic acid, 35158-39-5; *p*-chlorophenyl-4-oxo-3-bromobutanoic acid, 49780-08-7; *p*-anisyl-4-oxobutanoic acid, 3153-44-4; *p*-chlorophenyl-4-oxobutanoic acid, 3984-34-7; *p*-fluorophenyl-4-oxobutanoic acid, 366-77-8; 2-bromolaevulinic acid, 63104-98-3; 4-oxopentenoic acid, 4743-82-2; *p*-chlorophenyl-4-oxo-3-hydroxybutanoic acid, 60717-53-5; dibenzoylbromoethane, 63104-99-4; dibenzoylethylene, 4070-75-1; hydrogen bromide, 10035-10-6; *p*-OCH_3PhCH_2COOH, 104-01-8; CH_3COOH, 64-19-7; Me_2SO, 67-68-5; maleic anhydride, 108-31-6; benzene, 71-43-2; fluorobenzene, 462-06-6; chlorobenzene, 108-90-7; bromobenzene, 108-86-1; nitrobenzene, 98-95-3; toluene, 108-88-3; anisole, 100-66-3; succinic anhydride, 108-30-5.

References and Notes

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(10) *p*-OCH_3PhCH_2COOH, $K_a = 3.3 \times 10^{-5}$; CH_3COOH, $K_a = 1.7 \times 10^{-5}$.

(11) (a) Me_2SO-d_6, dried on molecular sieves, contained a trace of water gas chromatographically determined. (b) 4-(*p*-Substituted phenyl)-4-oxo-3-hydroxybutanoic acids were precipitated from reaction mixture by H_2O, isolated, and identified by mass and NMR spectroscopy. The mechanism of this reaction has not been the object of the present work, but the kinetic behavior of the reaction showed that the addition of H_2O has no influence on the rate.

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(15) It is noteworthy that acid catalysis, without deuterium change, takes place when some DCl is added to the reaction mixture ($^1/_4$ mol of DCl for 1 mol of product). In the equimolar mixture of DCl and product it is clear that CL^-Br^- exchange takes place. No catalytic effect on the elimination reaction was produced by CF_3COOH and by other organic acid. All experiments are reproducible on the methyl ester of each butanoic acid used.

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