Effects of Bromine Substituents on Rates of Acetate-promoted Enolization of Ketones

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Effects of bromine substituents on rates of acetate-catalyzed bromination of ketones are reported. Approximate polar contributions to the rates were obtained, based on the approximation that the steric effects of bromine and methyl are identical. Such polar substituent effects are quite large at the α′-position of an α-bromo ketone, leading to the conclusion that the carbonyl group is much better than the methylene group in transmitting polar effects.

Rate enhancements caused by α-bromine substituents are largely entropic in origin and rates correlate well with ionization constants of α-bromo acids. These results are interpreted as indicative of an enolate-like transition state for acetate-catalyzed enolization.

Les effets des substituants brome sur les vitesses de bromation des cétones, catalysée par l'acétate, sont rapportés. Les contributions polaires approximatives aux vitesses sont obtenues, fondées sur l'approximation que les effets stériques du brome et du méthyle sont identiques. De tels effets polaires de substituants sont très accentués sur la position α′ d'une α-bromo cétone permettant de conclure que le groupe carbonyle est de deux fois environ aussi bon que le groupe méthylène, dans la transmission des effets polaires. Les accroissements de vitesse dûs aux substituants α bromés sont grandement d'origine entropique et les vitesses sont en relation avec les constantes d'ionisation des α-bromoacides. L'interprétation de ces résultats révèle un état de transition du type énolate dans l'énolisation catalysée par l'acétate.

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Introduction

It has been known for a long time that most α-halo ketones are enolized more rapidly than simple ketones in the presence of base (1). In acetate-catalyzed iodination at 25°, chloroacetone and bromoacetone were reported to be 45.8 and 75.0 times as fast, respectively, as acetone (2) and acetate-catalyzed α-hydrogen exchange of chloroacetone at 41.8° was found to be about 580-fold faster than exchange of acetone (3). For the alkyl, aryl ketones $C_6H_5COCH_3$, $C_6H_5COCH_2Br$, and $C_6H_5COCHBr_2$, relative acetate-catalyzed bromination rates were reported to be 1:53:104 (4), statistically corrected. The success of the iodoform reaction (5) and of haloform reactions in general, has been attributed to fast halogenation of a first-formed halo ketone at the already-halogenated α-site (6–9).

Exceptions to the general rule are found in systems with sterically-hindered α-sites. For example, α-bromobenzyl phenyl ketones are brominated more slowly than the parent ketones in the presence of acetate (10) and 2-bromo-2,4-dimethyl-3-pentanone is less reactive toward hydroxide ion than 2,4-dimethyl-3-pentanone (11).

Greater reactivity of a halo ketone, relative to that of the parent ketone, was first attributed to an enhanced rate of enolization at the substituted α-site alone rather than to greater reactivity at both α-sites. This rationale was no doubt based on the findings that unsymmetrical halogenation of acetone in basic solutions is preferred (6), that the haloform reaction yields primarily halogen-free carboxylic acid (12, 13), and on the expectation that the carbonyl group would effectively insulate the remote α-position from the polar effect of α-halogen (14). Indications that both α-positions may have their reactivity enhanced came from the finding that α-halo acids are formed in haloform reactions (7, 8), albeit in low yield, and from measurements of hydrogen isotope exchange rates (3, 15). The latter work indicates that α-chlorine enhances acetate-promoted α′-enolization rates by factors ranging from about 4.4 (methyl-α-chlorobenzyl ketone) to 19 (chloroacetone), with the effect in α-chlorocyclohexanone intermediate at 5.1. In the case of α-fluorine substituents the rate enhancement is actually larger at the unsubstituted α-position. Fluoroacetone is exchanged about 3.5 times as

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fast as acetone in aqueous acetate buffer but the CH_3 group is 5.2 times as reactive as the CH_2F group, statistically corrected (3, 15).

In this article we discuss quantitative estimates of the polar effect of α-bromine substituents on rates of acetate-catalyzed enolization of ketones. A correlation between rate constants in that reaction and acidity constants of carboxylic acids is also presented.

Methods

Brominations were carried out in homogeneous media consisting of aqueous acetic acid–acetate buffer (1:10; 1 *M* in AcO^-) and dioxane (5% v/v). Reactions were pseudo-first-order; acetate being present in large excess over Br_2. All rates reported are for reactions of zero order in Br_2; that is, the bromine concentration range always exceeded the limit, *ca.* 10^{-5} -10^{-6} *M*, below which ketone bromination becomes first order in bromine (16). The overall rate of bromine consumption could therefore be equated to the overall rate of enolization. In the buffer medium employed, most of that enolization must be effected by acetate ions since catalysis by HOAc is not detectable in 1:10 (HOAc:OAc^-) buffer (17).

Enolization was followed by measuring the concentration of bromine via the redox potential of the medium, as described elsewhere (18). The method is sensitive to impurities which consume bromine and hence all ketones were checked by g.l.p.c. and were purified by preparative g.l.p.c. The shapes of graphs of relative bromine concentrations against time and the methods and equations for extracting rate constants from such data are described elsewhere (18).

Results and Discussion

To separate polar effects from steric effects, advantage was taken of the approximately equal steric requirements of methyl and bromine substituents. The steric substituent parameters (E_s) and the Van der Waals radii of Br and CH_3 are essentially the same (19). Therefore any consequence of interchanging the two substituents should be primarily the result of the difference in their inductive effects.

Table 1 contains kinetic data for the bromination of three sets of ketones. In the first set, successive substitution of bromine for methyl groups keeps the substrates sterically equivalent and rate factors therefore give a measure of the polar effect of α-bromine on α-enolization and on α′-enolization. Rate factors are of the order 780 and 92 at the α- and α′-sites, respectively, taking the corrected (bracketed) value in the second row. The value 8.0×10^{-5} M^{-1} s^{-1} for 1-bromo-2-butanone is the observed rate constant adjusted for a statistical factor of two. It is a crude value of the CH_2Br reactivity, based on the assumption that reaction at CH_3 can be neglected. The bracketed value includes a correction (see footnote to Table 1) for CH_3 reactivity.

The second set of ketones provides another measure of the α- and α′-effects. Again the effect of α-bromine is to enhance α′-reactivity by a factor near 10^3. A steric effect is introduced in going from $CH_3COC(CH_3)_3$ to $BrCH_2COC(CH_3)_3$ but that factor is known to be small compared to 10^3 (20). The second and third entries of set 2 are sterically equivalent and

TABLE 1. Rates of acetate-catalyzed enolization of ketones at 30°

Ketone	k^H (M^{-1} s^{-1})[a]	$\Delta\Delta G^*$ (kcal mol^{-1})[b]
$CH_3CH_2COCH_2CH_3$	9.4×10^{-8}	0.0
$CH_3CH_2COCH_2Br$	$8.0(7.3) \times 10^{-5}$[c]	4.1
$BrCH_2COCH_2Br$	6.7×10^{-3}	2.6
$(CH_3)_3CCOCH_3$	6.3×10^{-8}	0.0
$(CH_3)_3CCOCH_2Br$	5.8×10^{-5}	4.1
$(CH_3)_2CBrCOCH_2Br$	2.7×10^{-3}	2.3
$CH_3COC(CH_3)_3$	6.3×10^{-8}	0.0
$CH_3COCBr(CH_3)_2$	7.0×10^{-6}	2.8
$CH_3COCBr_2CH_3$	7.6×10^{-5}	1.5
CH_3COCBr_3	1.9×10^{-4}	0.5

[a]Statistically corrected. The statistical factors by which observed rate constants were divided are (starting with the top row): 4, 2, 4, 3, 2, 2, 3, 3, 3, and 3.

[b]In each set the difference between ΔG^* for that ketone and the one immediately above it, except in case of the first member of a set, which is taken as the reference compound for that set. The numbers are therefore increments in ΔG^* at 30° caused by the change in substituents. Values of ΔG^* were calculated from the equation

$$\ln k_{rate} = \ln \frac{kT}{h} - \frac{\Delta G^*}{RT}$$

[c]Based on the assumption that all enolization occurred at the CH_2Br group. The number in parentheses is the calculated CH_2Br reactivity obtained by correcting the observed rate for reaction at the other methylene group. The estimated rate for that group is 7.0×10^{-6} M^{-1}, s^{-1}, obtained by subtracting 2.6 kcal mol^{-1} from ΔG^* (observed). The equation $8.0 \times 10^{-5} = k^H_{CH_2Br} + k^H_{CH_2CH_3}$ was then applied.

again show that the effect of α-Br is also substantial (47-fold) on α′-reactivity.

In the third set of ketones the effects of one, two, and three α-bromines on α′-enolization rates of sterically-equivalent compounds are indicated. One bromine increases reactivity at the other α-site by the factor 111, compared to 92 and 47 in sets 1 and 2, respectively. A second and third bromine cause the much smaller factors 10.9 and 2.5, respectively, showing that the α-effects are far from cumulative.

The most striking result is that the polar effect of bromine is transmitted so well through the carbonyl group. The factor by which CH_2 groups attenuate inductive effects is about 2.8 per group intervening between the dipole and the carbon atom of interest (21). Therefore α′-substituents of halo ketones, which are insulated from the effect of α-halogen by two carbons, should see that effect attenuated by the factor 7.8 (*i.e.* 2.8^2). From the data of Table 1 we can calculate the actual insulating factor applicable to α′-substituents. It is given by $\log (k^{\alpha}_{Br}/k^{\alpha}_{H})/\log k^{\alpha'}_{Br}/k^{\alpha'}_{H}$, in which the ratio in the numerator is that for α-enolizations, with and without α-Br, while that in the denominator compares α′-enolizations, with and without α-Br. An equivalent expression is $\Delta\Delta G^{\ddagger}_{\alpha}/\Delta\Delta G^{\ddagger}_{\alpha'}$. The numerator is about 4.1 kcal mol^{-1} and the denominator is 2.8 or 2.3 kcal mol^{-1}, depending on the set of ketones chosen (Table 1). Thus we estimate the attenuation factor for α′-substituents to be only 1.3–1.8 compared to 7.8 calculated for two CH_2 groups. An attenuation factor below 2.8 indicates that the reactions from which that number was derived (21) are not perfect models for the systems in question here, in which the insulating group contains π-electrons.[2] Nevertheless, although we cannot assign a number to the CO component of the CH_2CO group, the small composite attenuation factor indicates that the carbonyl group is a very good transmitter of polar effects.

Although the effects of α- and α′-bromine are roughly additive (compare third, sixth, and eighth entries in $\Delta\Delta G^{\ddagger}$ column of Table 1) it is clear that the second and third halogens at a given α-site are much less effective than the first. Such lack of additivity is not new; it shows up also in the ionization constants of α-bromocarboxylic acids. In fact there is a good correlation between the pK_a values of some model acids, chosen because their pK_a values are known (22), and acetate-catalyzed enolization rate constants of corresponding bromo ketones (Fig. 1). The correlation coefficient is -0.995 and the slope of the line is -0.87 ± 0.02. This correlation suggests that the transition state for enolization is enolate-like although the extent to which negative charge is developed cannot be inferred from the slope. In a series of phenyl benzyl ketones the fractional charge developed in the ketone moiety at the transition state for acetate-catalyzed enolization was estimated to be 64% (23).

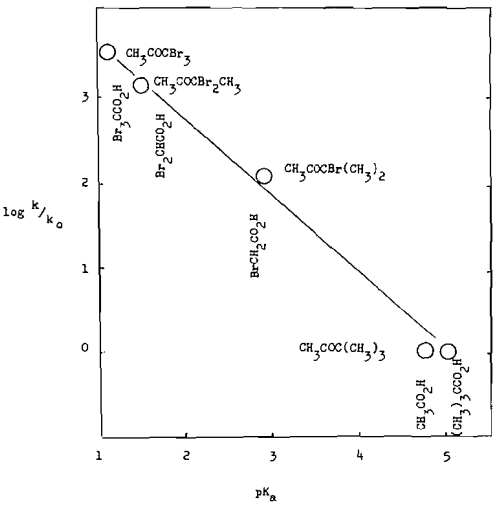


FIG. 1. Correlation of $\Delta G^{\ddagger}$ for enolization with ΔG^{0} for ionization.

Activation parameters found for acetone and bromoacetones (Table 2) are in keeping with an enolate-like transition state. For reaction at room temperature over half of the substituent effect of bromines is entropic. A likely way in which bromines increase the activation entropy is through their effect on solvation. A bromo enolate must be less solvation-dependent than an unsubstituted enolate because it can partly disperse charge internally into the polar C—Br bond. Consequently, for a given degree of charge development in an enolate-like transition state, bromine substituents should decrease the extent of solvent electrostriction.

[2]The minimum factor for the insulating unit $CH_2C{=}O$, assuming that CO transmits perfectly (attenuation of CO = 1), would be 2.8 × 1.

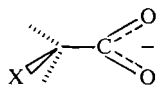
TABLE 2. Activation parameters of acetate-catalyzed enolization of acetone and bromoacetones

Ketone	CH_3COCH_3	CH_3COCH_2Br	$CH_3COCHBr_2$
k^H, [a] 20°	2.0×10^{-8}	9.1×10^{-5}	1.7×10^{-3}
25°	4.0×10^{-8}		
30°	7.4×10^{-8}	3.3×10^{-4}	5.1×10^{-3}
35°	1.3×10^{-7}		
40°	2.4×10^{-7}	8.3×10^{-4}	1.5×10^{-2}
ΔH^* (kcal mol^{-1})[b]	22.0 ± 0.3	19.6 ± 0.7	19.3 ± 0.4
ΔS^* (e.u.)[b]	-18.5 ± 0.6	-10.0 ± 2.0	-5.4 ± 1.0

[a]Statistically corrected second order rate constants (M^{-1} s^{-1}).
[b]From the equation $\ln k_{rate}/T = \ln k/h - \Delta H^*/RT + \Delta S^*/R$. Errors in the activation parameters came from root-mean-square errors in the slope and intercept of a computer-fitted line.

The charge in the ketone moiety at the transition state need not be increased by Br-substituents, for the more acidic α-bromo ketones must have more reactant-like transition states than the parent ketones (24).

A rationale for the non-cumulative effects of Br-substituents on either pK_a values or enolization rates is based on conformational preferences. An α-halo carboxylate ion (**1**)



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probably has a preferred conformation in which the C—X dipole is perpendicular to the carboxylate plane, as drawn. Such an arrangement should lead to the minimum dipole–ion repulsions. A second halogen cannot also adopt that arrangement and consequently the net inductive withdrawing effect per halogen would be reduced through a repulsive ion–dipole interaction. The argument for an enolate-like transition state is strictly analogous.

There is one problem with regard to the enolate-like transition state for catalysis of enolization by a weak base like acetate. 2-Butanone enolizes more slowly than acetone but its reactivity per hydrogen is higher at the methylene than at the methyl group (17, 25). One way of accounting for this is to postulate predominant steric retardation with a small polar rate enhancement at CH_2 superimposed. For an enolate-like transition state that effect would have to be one of electron-withdrawal, contrary to the effect of para CH_3 on benzoic acid acidity. Because of this problem we suggested (20) that the transition state might be enol-like, at least for the more highly endothermic enolizations involving weak bases. However, this concerted mechanism, originally postulated by Swain (26) to account for a termolecular term in the kinetics of enolization of acetone (27, 28) has little support as a general mechanism, although it may be important in carboxylic acid–carboxylate anion catalyst systems (29). Moreover, Brönsted correlations (30) indicate that the transition state for enolization of acetone by weak bases is highly enolate-like ($\beta \simeq 0.8$). Our present results are more readily rationalized in terms of transition states with enolate character but do not clarify the anomalous methylene reactivity of 2-butanone toward weak bases.

It should be emphasized, in summary, that it is probably unsafe to extrapolate the reactivity trends reported here. Although the effects of I, Br, and Cl may be qualitatively the same, fluorine- (16, 31) and methoxy-substituted (32) ketones do not fit expectations based on the inductive effects of those substituents. It has been suggested (33) that polarizability of the substituent may be a controlling factor. Furthermore the quantitative relationships between α- and α′-reactivity are no doubt functions not only of the base and the substituent but also of the medium and the temperature.

Experimental

Purification of Bromoketones

The general procedure involved rapid distillation, at reduced pressure, of a CCl_4 extract of the crude bromo ketone mixture obtained from the appropriate synthesis

(see below). The fraction shown (by n.m.r.) to contain most of the desired product was stabilized by addition of magnesium oxide, which removes traces of HBr, before it was subjected to preparative g.l.p.c. 1,1,1-Tribromoacetone was partly isomerized to 1,1,3-tribromoacetone on distillation. Consequently it was isolated by g.l.p.c. of the crude CCl_4 extract directly.

Preparative g.l.p.c. was done with a 10 ft × 3/8 in. silicone QF-1 column (10%, on 60/80 mesh, non-acid-washed, Chromosorb W) in a Varian Aerograph A90-P3 instrument. The column was operated at 110–130° with helium flow rates between 50 and 100 ml/min. Compounds collected from the column were rechromatographed at least once or until they appeared to be homogeneous on three different analytical columns (10 ft × 1/8 in. QF-1, 12%; 5 ft × 1/8 in. FFAP, 10%; and 10 ft × 1/8 in. SE-30, 20%; all on 60/80 mesh Chromosorb W) and showed only the expected n.m.r. signals. Such samples were water-white and stable when stored at about −10°, without added MgO.

N.m.r. spectra were recorded on a Varian T-60 instrument.

Bromoacetone

The method of Catch and coworkers (34), in which acetone is brominated in the presence of potassium chlorate, was used. The crude product contained chloroacetone, presumably from substitution on bromoacetone by chloride generated from chlorate, and 1,1-dibromoacetone. Purification by g.l.p.c., as described above, gave bromoacetone: n_D^{25} 1.4680 (lit. (35), n_D^{25} 1.4739, (33), n_D^{15} 1.4697); n.m.r. (CCl_4) δ 2.30 (s, 3, CH_3), 3.78 (s, 2, CH_2).

1,1-Dibromoacetone

1,1-Dibromoacetone was obtained as a byproduct from the synthesis of bromoacetone (above) and from the preparation of 1,1,1-tribromoacetone (below). Pure material (g.l.p.c.) had n_D^{25} 1.5232 (lit. (35) n_D^{25} 1.5237); d_4^{23} 2.063; n.m.r. (CCl_4) δ 2.51 (s, 3, CH_3), 5.67 (s, 1, CH).

1,1,1-Tribromoacetone

1,1-Dibromoacetone (2.81 g, 0.013 mol) and *N*-bromosuccinimide (NBS) (2.32 g, 0.013 mol) were refluxed in CCl_4 (14 ml) under illumination from a 75 W tungsten spot lamp. After 12 h, the yield was 91%, estimated by n.m.r. Chromatography as described above gave pure tribromoacetone: n_D^{25} 1.5708 (lit. (35) n_D^{25} 1.5689); d_4^{20} 2.334; n.m.r. (CCl_4) δ 2.76 (s, CH_3).

1,1-Dibromoacetone was also prepared from NBS and acetone and by bromination of acetone with Br_2 in glacial acetic acid containing sodium acetate. These procedures were less satisfactory in our hands and are therefore not described in detail.

1,3-Dibromoacetone and 1,3-Dibromo-3-methyl-2-butanone

These compounds were prepared by the method of Wagner and Moore (36). The appropriate ketone (0.5 mol) in a 250 ml, three-necked flask fitted with gas inlet tube, magnetic stirrer, pressure-equalizing dropping funnel, and a reflux condenser was cooled with ice while bromine (53 ml, 1 mol) was added gradually from the funnel. Reaction was initiated with the light from a tungsten lamp when a few drops of Br_2 had been added; the rest of the Br_2 was then dropped in over a period of 2 h. When addition was complete nitrogen was bubbled through the solution overnight to sweep out HBr. The product was distilled from the flask at low pressure and chromatographed as described. From acetone was obtained 1,3-dibromoacetone: m.p. 28–28.5°; b.p. 80°, (lit. (35) m.p. 25.5–27.0°, b.p. 79.5–80.5 (9 mm)); n.m.r. (CCl_4) δ 4.10 (s, CH_2). Methyl isopropyl ketone gave 1,3-dibromo-3-methyl-2-butanone: m.p. 13–14°; b.p. 68–72° (3 mm); n_D^{25} 1.5154 (lit. (36) m.p. 10–12°, b.p. 111° (15 mm), n_D^{25} 1.5178); n.m.r. (CCl_4) δ 1.94 (s, 6, CH_3), 4.31 (s, 2, CH_2).

1-Bromo-2-butanone

1-Diazo-2-butanone was treated with HBr according to the procedure of Catch and coworkers (37) to afford the title compound: b.p. 44–45° (10 mm); n_D^{25} 1.4670 (lit. (34) b.p. 49° (10 mm), lit. (37) n_D^{20} 1.4670); n.m.r. (CCl_4) δ 1.08 (t, 3, $J = 7$ Hz, CH_3), 2.64 (q, 2, $J = 7$ Hz, CH_3CH_2), 3.76 (s, 2, $BrCH_2$).

3-Bromo-3-methyl-2-butanone

This ketone was synthesized from methyl isopropyl ketone by the method of Catch and coworkers (38) and was purified by g.l.p.c.: n_D^{25} 1.4554, (lit. (39) n_D^{25} 1.4510); d_4^{20} 1.334; n.m.r. (CCl_4) δ 1.80 (s, 6, $(CH_3)_2C$), 2.36 (s, 3, CH_3CO).

3,3-Dibromo-2-butanone

2-Butanone (7.2 g, 0.1 mol) and NBS (35.6 g, 0.2 mol) were refluxed in CCl_4 (150 ml) under illumination from a 75 W tungsten spot lamp (39). After $1\frac{1}{2}$ h the reaction was complete and the yield (n.m.r.) of the title compound was about 95%. Distillation followed by preparative g.l.p.c. gave pure 3,3-dibromo-2-butanone: n_D^{25} 1.5053 (lit. (39) n_D^{25} 1.5050); d_4^{22} 1.827; n.m.r. (CCl_4) δ 2.50 (s, CH_3CO), 2.67 (s, 3, CH_3CBr_2).

1-Bromo-3,3-dimethyl-2-butanone (Bromopinacolone)

Pinacolone (10.02 g, 0.1 mol) and NBS (17.8 g, 0.1 mol) in CCl_4 (100 ml) were heated and irradiated with the light from a 75 W tungsten spot lamp. After 24 h of refluxing, the solution contained pinacolone (70%), bromopinacolone (15%), and dibromopinacolones (15%), as estimated by n.m.r. The mixture was cooled with ice, the insoluble solids were filtered off, and the solution was concentrated on a rotary evaporator. Distillation gave a fraction boiling at 55–60° (4 mm) which contained at least 50% 1-bromo-3,3-dimethyl-2-butanone (n.m.r.) along with $(CH_3)_3CCOCHBr_2$, $BrCH_2(CH_3)_2CCOCH_3$, and $BrCH_2(CH_3)_2CCOCH_2Br$. The desired ketone was purified by g.l.p.c. as described above: n_D^{25} 1.4630 (lit. (40) n_D^{25} 1.4659, (41) n_D^{20} 1.4640); n.m.r. (CCl_4) δ 1.21 (s, 9, $(CH_3)_3C$), 4.01 (s, 2, $BrCH_2$).

Other Ketones

Acetone, butanone, and 3-pentanone were commercial, reagent-grade materials distilled in a 20 × 2 cm glass still packed with 3 mm single-turn glass helices. Center cuts showed only the expected n.m.r. signals and only a single peak on analytical g.l.p.c. columns.

Pinacolone (Aldrich, reagent grade) was purified by preparative g.l.p.c., as described above for bromo ketones. The product used was homogeneous on three analytical g.l.p.c. columns and there were no impurities detectable by n.m.r.

Procedure

The apparatus and the procedure are described elsewhere (18).

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