A Method for Determining Relative Rates of Reaction of Halogenating Agents with Enols

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Abstract: The variation in ratios of 3-halo:1-halo product has been studied as a function of the per cent H_2SO_4 for the reaction of 2-butanone with Cl_2, Br_2, and two *N*-chloro amines. In dilute acid, all give the same ratio (~2.6) confirming that enolization of the 2-butanone is rate determining. The ratio shifts to a new limiting value as the per cent H_2SO_4 is increased because the reaction of enol with halogenating agent becomes rate determining. A method for determining relative rates of reaction of halogenating agents with enols is developed.

It is well established that the α-chlorination and α-bromination of ketones in dilute acids proceeds by a rate-determining enolization.[1-3] The rate law is eq 1. It is evident that the rate law could change to eq 2 (rate-determining reaction of enol with halogenating agent) if (1) an inactive halogenating agent were used whose rate of attack on enol was slow, (2) the concentration of halogenating agent was made very small,[2] and (3) the level of acidity was increased to make the keto–enol equilibration rapid.[4]

$$d[\text{product}]/dt = k_1[\text{ketone}][H^+] \qquad (1)$$

$$d[\text{product}]dt = k_2[\text{ketone}][\text{halogenating agent}] \qquad (2)$$

The changeover in mechanism from eq 1 to eq 2 would be signaled by a change in the ratio of the two α-halo products from one limiting value to a new limiting value. For the chlorination and bromination of 2-butanone with Cl_2 and Br_2, this phenomenon has been observed for changing halogen concentration and for varying H_2SO_4 concentration.

Table I shows the variation in the ratio of 3-halo:1-halo product as the per cent H_2SO_4 is varied. At low acidity (10% H_2SO_4) the ratio of 3-Cl:1-Cl and the ratio of 3-Br:1-Br were effectively equal (2.1 and 2.4), confirming that the reaction was a rate-determining enolization in which the product ratio is independent of halogenating agent and is determined by the relative rate of formation of the two enols. As the per cent H_2SO_4 was increased, the product ratio varied analogously to a pH–rate profile and exhibited an inflection point. This inflection point occurred at about 35% H_2SO_4 for Cl_2 and at about 45% H_2SO_4 for Br_2. These inflection points are for an average value of the halogen concentration (0.006 *M*) rather than the initial concentration (0.0125 *M*) since the halogen concentration decreases during the reaction and is zero at completion.

Table I. Chlorination and Bromination of 2-Butanone at 25° in Aqueous Sulfuric Acids[a]

% H_2SO_4	3-Cl:1-Cl	% H_2SO_4	3-Br:1-Br
10	2.1[b]	10	2.4[c]
30	3.0	20	2.4
32	4.8	40	4.0
35	5.3	50	7.3
40	9.0	60	11.5
50	10.1	70	11.5
80	8.1		
96	9.1		

[a] The initial concentration of 2-butanone was 0.025 *M* and the initial concentrations of Cl_2 and Br_2 were 0.0125 *M*. [b] A ratio of 2.6 was reported for chlorination in aqueous HCl.[3] [c] A ratio of 2.7 was reported for bromination in dilute acid: H. M. Cardwell and A. E. Kilner, *J. Chem. Soc.*, 2430 (1951).

The expected effect of varying halogen concentration was also demonstrated. Since this effect is largest around the inflection point, 32% H_2SO_4 was chosen for the Cl_2 experiments and 50% H_2SO_4 for the Br_2 experiments. Doubling the initial amount of Cl_2 lowered the 3-Cl:1-Cl ratio from 4.8 to 2.3 whereas halving the initial amount of Cl_2 raised the ratio from 4.8 to 7.4. Similarly, doubling the initial Br_2 concentration lowered the 3-Br:1-Br ratio from 7.3 to 6.7 whereas halving the initial Br_2 concentration raised the ratio from 7.3 to 8.1.

The reactions were conducted to 25% completion to reduce dichloro products. Distillation of the ether extractable products established a material balance and showed that only unreacted 2-butanone and the two monochloro-2-butanones were produced (see Experimental Section).

The difference in the inflection points for Cl_2 and Br_2 can be used to estimate ratio of rate constants (k_2 in eq 2) for Cl_2 plus enol and Br_2 plus enol. At the inflection point, the rates of eq 1 and 2 are equal so that the right-hand sides of these two equations can be set equal, eq 3 and 4. Equations 3 and 4 can be combined to give eq 5 since k_1 is the same for both Cl_2 and Br_2 and cancels, since the ketone concentration term cancels, and since concentrations of Cl_2 and Br_2 were deliberately made equal. There is some question as to how to evaluate the change in $[H^+]$ from 35 to

$$k_1[\text{ketone}][H^+ \text{ in } 35\%\ H_2SO_4] = [k_2 \text{ for } Cl_2][\text{ketone}][Cl_2] \qquad (3)$$

$$k_1[\text{ketone}][H^+ \text{ in } 45\%\ H_2SO_4] = [k_2 \text{ for } Br_2][\text{ketone}][Br_2] \qquad (4)$$

$$k_2 \text{ for } Br_2/k_2 \text{ for } Cl_2 = [H^+ \text{ in } 45\%\ H_2SO_4]/[H^+ \text{ in } 35\%\ H_2SO_4] = 6.2 \qquad (5)$$

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[1] A. Lapworth, *J. Chem. Soc.*, **85**, 30 (1904).

[2] R. P. Bell and K. Yates, *ibid.*, 1927 (1962).

[3] C. Rappe, *Acta Chem. Scand.*, **21**, 857 (1967). This paper lists references to discussions of this subject in reviews and texts.

[4] L. Zucker and L. P. Hammett [*J. Amer. Chem. Soc.*, **61**, 2791 (1939)] showed that the rate of iodination of acetophenone became dependent on the concentration of iodine at acidities greater than 50% H_2SO_4.

Table II. Chlorination of 2-Butanone with *N*-Chlorodimethylamine and *N*-Chlorodiisopropylamine at 25° in Aqueous Sulfuric Acids[a]

%	3-Cl:1-Cl ratio	
H_2SO_4	Me_2NCl	$(2\text{-}Pr)_2NCl$
10		2.5
20	2.6	2.6
30	2.6	2.6
40	2.6	2.7
50		5.3
60	19.0	19.0
70		19.0

[a] The initial concentration of 2-butanone was 0.025 *M* and the initial concentration of R_2NCl was 0.0125 *M*.

45% H_2SO_4. We have chosen to use the antilog of the Hammett H_0 acidity function. The values of H_0 in 35 and 45% are 2.06 and 2.85[5] from which it can be calculated that Br_2 reacts 6.2 times faster with the enols than Cl_2. Since the interior enol (2-buten-2-ol) is predominantly attacked, this ratio is essentially that for attack on the interior enol. However, the limiting ratio for Cl_2 (9–10) is close to that for Br_2 (11.5) so that the two enols have about the same rate ratio for attack by Cl_2 relative to attack by Br_2. The estimate assumes no changes in k_2 between 35 and 45% H_2SO_4.

Chlorination of 2-butanone by Me_2NCl and $(2\text{-}Pr)_2NCl$ shows the same 3-Cl:1-Cl ratio as Cl_2 in 10–20% H_2SO_4 (Table II). This again confirms that the product ratio is dictated by the relative rate of formation of the two enols. The data in Table II allow only a rough estimate of the inflection point, about 55% H_2SO_4 for both *N*-chloro amines. This calculates out to the R_2NHCl^+ species chlorinating the enols (predominantly the interior enol) 11 times faster than Br_2.

Sulfuryl chloride (SO_2Cl_2) has been recommended for selective chlorination of ketones. For 2-butanone, the ratio of 3-Cl:1-Cl is 10–20:1.[6] With 2-methylcyclohexanone, 80–85% yields of 2-chloro-2-methylcyclohexanone were reported.[7] Since comparable ratios have been obtained with Cl_2 in 40–96% H_2SO_4 and Br_2 in 60–70% H_2SO_4 (Table I), we suggest that the selectivity exhibited by SO_2Cl_2 is not due to any special selectivity of SO_2Cl_2. Instead, SO_2Cl_2 reacts with the two enols at relative rates similar to those for Cl_2 and Br_2. The selectivity exhibited is a result of (1) a slower rate of reaction with enol and/or (2) catalysis of the keto–enol equilibration caused by HCl generated in the chlorination, perhaps augmented by adventitious H_2SO_4.

High ratios (15–40:1) of 3-Br:1-Br have been reported for the bromination of 2-butanone by *N*-bromosuccinimide and by HOBr. The reactions were regarded as free-radical processes based on catalysis by light.[8] This view is supported by the following observation. 2-Butanone was treated with *N*-bromosuccinimide in refluxing CCl_4 (76°) with and without irradiation by a 300-W tungsten lamp. With irradiation a 25:1 ratio of 3-Br:1-Br was produced (at 50% conversion) as found by Rappe.[8] In the dark, the ratio was 1.3:1, a profound difference.

2-Butanone was also chlorinated in 10–70% H_2SO_4 with *N*-chloro-*N*-methylmethanesulfonamide and *N*-chloro-*N*-*tert*-butylmethanesulfonamide. In 10–50% H_2SO_4, the 3-Cl:1-Cl ratio was 10–13. It does not seem that a rate-determining enolization was involved. If it had the ratio would have been ~2.6. In 60–70% H_2SO_4, the 3-Cl:1-Cl ratio increased to 24. Superficially, this indicates an inflection point at ~55% H_2SO_4 which would make the *N*-chloro amides about as active as the *N*-chloroammonium ions. This conclusion is invalidated by the abnormal ratios in dilute acids.

Experimental Section

2-Butanone + Cl_2. 2-Butanone (0.1 mol) was dissolved in 250 ml of the aqueous sulfuric acid. The Cl_2 (0.05 mol) was added by attaching a flask of the liquid Cl_2 and flashing it into the vigorously stirred acid by heating with warm water. The addition took ~1 min and the reaction was complete in 1 hr. The sulfuric acid was diluted to 10% and extracted with ether. The ether extract was washed with 10% aqueous Na_2CO_3 and dried with $MgSO_4$. Removal of the ether by distillation left 9.5 g of product. Since it was well established that the products were 1- and 3-chloro-2-butanone,[3] the mixture was directly analyzed by gas chromatography. A 6 ft × 0.25 in. glass U column was used in a series 5000 Barber-Colman instrument with a flame ionization detector. The packing was 10% tricresyl phosphate on 80–100 mesh Gas Chromosorb W[9] and the operating temperature was 85°. The relative retention times of 2-butanone, 3-chloro-2-butanone, and 1-chloro-2-butanone were 1:2.76:6.06. No significant amount of dichloro products was seen.

2-Butanone + Br_2. The reaction was conducted the same as with Cl_2 except that the Br_2 was directly added as the liquid. The products have been shown to be the 1- and 3-bromo-2-butanones (footnote *c*, Table I). Relative retention times at 120° of 2-butanone, 3-bromo-2-butanone, and 1-bromo-2-butanone were 1:2.75:4.53. No significant amount of dibromo products was seen.

Preparation of Halogenating Agents. *N*-Chlorodiisopropylamine was prepared by mixing equimolar diisopropylamine and aqueous NaOCl at 0–5°. After the mixture was stirred for 30 min, the organic layer was separated, washed with 5% aqueous H_2SO_4, and used without further purification. It is >95% pure by nmr.

N-Chlorodimethylamine was prepared in a manner similar to that reported.[10]

N-Methylmethanesulfonamide (from methanesulfonyl chloride and 40% aqueous methylamine) had bp 78–79° (0.03 mm) as reported.[11] The amide crystallized from the aqueous solution during formation and was washed with 10% aqueous HCl and water before distillation. The nmr spectrum in $CHCl_3$ consisted of singlets (3 H) at δ 2.75 and 3.05 and a broad band (H) at δ 5.44.

N-Chloro-*N*-methylmethanesulfonamide was prepared by stirring equimolar *N*-methylmethanesulfonamide and *N*-chlorosuccinimide in ether in place of the *tert*-butyl hypochlorite method.[11] After 1 hr, the succinimide was removed by filtration and the ether solution washed with water. Evaporation of the ether gave the *N*-chloro product, mp 32–33° (lit.[11] mp 32–33°). The nmr spectrum in $CHCl_3$ consisted of singlets of equal area at δ 3.31 and 3.52.

N-*tert*-Butylmethanesulfonamide, mp 38–40° (lit.[11] mp 40–41°), was prepared from the sulfonyl chloride and the amine.[11] The nmr spectrum in $CHCl_3$ consisted of singlets (3 H and 9 H) at δ 2.95 and 1.40. It was chlorinated with *N*-chlorosuccinimide in ether to produce the *N*-chloro-*N*-*tert*-butylmethanesulfonamide.[11] Attempted distillation of this product resulted in decomposition. The nmr spectrum in $CHCl_3$ consisted of singlets (3 H and 9 H) at δ 3.15 and 1.48 and served to identify the product and show that it was >90% pure.

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