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The Acetate-catalyzed H – D Exchange of Some Simple Chloroketones

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The kinetic acidities of some simple chloroketones have been measured by the rate at which they incorporate deuterium from D_2O/acetic acid-d_4 in the presence of acetate ion. The overall kinetic acidity of a ketone is generally increased by chlorine substitution α to the carbonyl group, however, proton exchange does not necessarily occur preferentially at the site of substitution. The implications of these results for studies of rates of base-catalyzed halogenation in structurally encumbered ketones are discussed.

In their classic study of proton mobility in substituted acetones, Bell and Lidwell [1] examined among other ketones, the three haloketones: monobromoacetone and monochloroacetone (zero-order rates of iodination), and 1,1-dichloroacetone (zero-order rate of bromination). The results together with the work of Watson and Yates [2] provided the strongest experimental basis for the assumption that the introduction of the first halogen following a rate determining proton abstraction was followed by rapid substitution of additional halogen at the same position when this was possible. That is, introduction of a halogen on the carbon α to the carbonyl group influences the reactivity of the protons on that carbon toward a base to a much greater extent than for the carbon-bound protons α′ to the carbonyl group. Isolation of the products of the bromination of 1,1-dibromoacetone in 75 % acetic acid [2] and of certain unhalogenated acids resulting from the haloform reaction of methyl ketones under basic conditions [3] support this presumption.

However, it was soon recognized that this was not always the case.[4] In particular, the bromination of β-diketones gave rise to complex kinetics which could be analyzed for rate constants for sequential halogenation (proton removal) at the central methylene group. The introduction of the first and second halogen were found to occur at comparable rates, which was explained by the special characteristics of charge delocalization in the anions of β-

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diketones.[4] In general, one might expect that structural changes in *any* ketone may result in cases where substitution of the first halogen may occur competitively in both positions (α and α′)* where these positions are nonequivalent (as would indeed be observed for most ketones [5]) and substitution of the second halogen may occur at the other α-position. Furthermore, the polyhalogenation of a given position may not go to completion.[6] Thus Schellenberger and Hübner [7] have found only monoiodination in 2-butanone.

More recently, both Rappe,[8–10] Jullien and co-workers,[11–13] and Bell and co-workers [14,15] have extensively studied proton mobility in α-haloketones with the aid of NMR and mass spectroscopy, and halogenation, respectively. The present study arose as an elaboration of these investigations and, independently, to shed additional light on the factors surrounding the mechanisms of the Favorskii rearrangement and the halogenation of ketones.

We have studied the acetate-catalyzed deuteration of a series of five chloroketones at 42°C by NMR spectroscopy. These were monochloroacetone, 1,1-dichloroacetone, 1-chloro-2-butanone, 3-chloro-2-butanone, and 3-methyl-3-chloro-2-butanone. In order to avoid interference from solvent peaks, we used a buffer composed of sodium acetate-d_3 and acetic acid-d_4. The results are reproduced in Table 1. Preliminary attempts to study monobromoacetone were frustrated because of competitive S_N2 attack of acetate to give the acetoxyketone; *vide infra*.

RESULTS AND DISCUSSION

A. S_N2 Displacement of chloride by acetate. To determine whether S_N2 displacement of chloride by acetate might be a competing base and ketone destroying side reaction, a parallel study was made, using an isotopically unsubstituted buffer solution of composition similar to that used for the proton exchange studies. With the exception of 1,1-dichloroacetone and 3-methyl-3-chloro-2-butanone, the presence of an important side reaction was detected. That it was S_N2 displacement of chloride by acetate was deduced from the number of new peaks (three in the case of chloroacetone) that developed, their relative intensities, their chemical shifts relative to the parent ketone, and the fact that chloro- and bromoacetone gave rise to a common product. This side reaction has been observed previously in acetate buffers.[16] The substituted ketones were not isolated. The reaction could be followed by integration of the peak due to the protons geminal to chlorine and a kinetic analysis made. If the initial ketone concentration is not carefully chosen to be equal to the acetate concentration, the integrated expression

$$\frac{1}{B_0 - A_0} \ln \left\{\frac{A_0 B}{B_0 A}\right\} = kt \qquad (1)$$

must be used,[17a] where B_0 and A_0 are the initial concentrations of ketone and acetate, respectively, and B and A their concentrations at time t. Because of the relatively large uncertainty in the integral value (> 3 %) and hence

* The α- and α′-positions refer to the carbon atoms α to the carbonyl group in the ketone, unless specified otherwise.

concentration of B (and thereby A) and the particular nature of the logarithmic expression, the scatter in the kinetic plot was very great. If, however, the initial concentrations of acetate and ketone are chosen to be equal, the integrated rate expression is [17b]

$$\frac{1}{B} - \frac{1}{B_0} = kt \qquad (2)$$

which is less sensitive to experimental error. All the plots were linear *within experimental error*, but were still far from satisfactory. It is emphasized, therefore, that the bimolecular rate constants given in Table 2 are orders of magnitude *only*.

The results are of particular significance for the proton exchange kinetics only for the slower rates of exchange, where $k_{obs} < 3 \times 10^{-5}$ sec^{-1}. A rough calculation shows, for example, that *ca.* 18 % acetate and 11 % ketone have been converted to the α-acetoxyketone after one half-life of exchange at the methyl group of chloroacetone. The corresponding figures after one half-life of exchange at the methylene group are roughly 1 % and 0.7 %, respectively. The primary source of interference due to the S_N2 reaction is destruction of catalyst and ketone. This is, however, a relatively slow process, so that it may be neglected for initial rates of H–D exchange. For the same reason, any complications due to the production of, and eventual H–D exchange reactions in the resultant acetoxyketone may be neglected. Rate constants for slowly exchanging groups are therefore evaluated from the initially linear portions of a logarithmic plot. This constituted up to 30 % exchange at the

Table 1. Acetate-catalyzed H–D exchange at 42°C.

Ketone	Concentration (mol/l)	$nk_{CHn} \times 10^6$ sec^{-1}			K_D[a]
		CH_3	CH_2	CH	
Chloroacetone	1.53	17.8 ± 2.4 (27)[b]	360 ± 48		20 ± 4 (14)[b]
1,1-Dichloroacetone	1.26	127 ± 7		1490 ± 170	11.7 ± 1.4
1-Chloro-2-butanone	1.25		175 ± 50[c] 8.6 ± 1.2[d]		20 ± 5[e]
3-Chloro-2-butanone	1.19	15.5 ± 2.4		5.5 ± 1.5	0.35 ± 0.1
3-Methyl-3-chloro-2-butanone	0.76	3.1 ± 0.3			
2-Butanone[f]		1.7	1.2		0.7

[a] $K_D = (nk_{CHn}/3k_{CH3})$.
[b] The value in parentheses takes into account the influence of an assumed isotope effect of 6 on the initial rate of exchange (see Ref. 18).
[c] Refers to CH_2Cl.
[d] Refers to CH_2CH_3.
[e] Refers to $(2k_{CH2Cl}/2k_{CH2CH3})$.
[f] Roughly estimated values from a single experiment.

respective positions. Plots for the more reactive positions were linear for up to 2 – 3 half-lives. An analysis of additional sources of non-linearity in logarithmic plots of primary data for H – D exchange studies is presented in detail elsewhere.[18]

B. Exchange results. It is apparent from Table 1 that the protons α to a chlorine atom are not necessarily kinetically more acidic than protons in an unchlorinated substituent, but, rather, the kinetic acidity is a function both of the inductive effect of chlorine and what may be diffusely called "steric effects". If one thinks of chloroacetone as a model compound and examines the effect of adding substituents to the model, a number of observations are possible. Introduction of a second chlorine atom (1,1-dichloroacetone) increases the acidity of the remaining proton α to the chlorines (*per hydrogen* rate constant) by a factor of *ca.* 8. The kinetic acidity of the α′-methyl group is similarly increased by a factor of 7. Thus introduction of a halogen at one of the α-carbons may in some cases markedly increase the reactivity of the protons on the α-carbon. In exploratory work under conditions similar to those of this investigation, however, Jullien and Nguyen have reported relative rates of H – D exchange at the methylene and methyl groups in chloroacetone which differ from ours by a factor of *ca.* 4 – 5.[11,13] Some of the discrepancy may be explained by the fact that rates of H – D exchange for a given group in a ketone in which the other α-position exchanges much more rapidly are probably "underdetermined" due to the presence of unrecognized isotope effects.[18] This is not a problem in their method of measurement, but then there is large uncertainty in the determination of the relative rates of exchange (± 40 %), because subtraction of two large quantities is necessary to obtain the slower rate of methyl exchange.[11,13,19] We estimate for an isotope effect of 6 in the absence of an equilibrium isotope effect that our methyl rate in chloroacetone is too small by a factor of *ca.* 1.5. Thus the discrepancy may well lie in the errors, systematic and statistical, inherent in the different methods of measurement as well as the slight difference in experimental conditions. In a more detailed investigation carried out in dilute acetate buffer, however, these workers have reported errors not in excess of ± 10 %,[13,19] but since evidence was also obtained for the intervention of complex salt effects, further comparison of results is not possible. In any case, the protons α to chlorine in chloro- and 1,1-dichloroacetone are (much) more acidic than the methyl protons, and hence the respective rates of iodination and bromination of these ketones[1] should be a good measure of the kinetic acidities of these protons alone. Indeed, the rate ratio determined by halogenation (acetate catalysis) is *ca.* 10 (*per hydrogen*), while our result is 8. This smaller value is expected on the basis of the temperature difference alone in the two studies (25°C and 42°C, respectively), providing the difference in the entropies of activation is negligible.

Substitution of a methyl group on the α′-methyl group of chloroacetone (1-chloro-2-butanone) has a negligible effect on the acidity of the remaining two protons. On the other hand, the acidity of the protons α to chlorine is decreased by a factor of 2, presumably because of increased steric hindrance in the near planar enol(ate)-like transition state.

Substitution of a methyl group for one of the protons α to chlorine in chloroacetone (3-chloro-2-butanone) results in a decrease in the kinetic acidity of the remaining proton by a factor of *ca.* 30. The acidity of the α′-methyl group is little affected. Examination of the K_D-value for this ketone indicates that 3-chloro-2-butanone (and 2-butanone as a result) is a case where halogenation data might give rise to deviation from linearity in first-order (log-time) or zero-order (concentration-time) plots, depending on the initial conditions. Thus, if in the halogenation of 2-butanone, the first halogen enters the 3-position (H – D exchange occurs competitively at both positions, while in halogenation the 3-position appears to be favoured by a factor of 6 over the 1-position),[16] the second halogen will not be preferentially introduced at the same carbon, but rather into the methyl group. But if the first halogen enters the methyl group, at least one more halogen will be rapidly substituted at the same position (*cf.* 1-chloro-2-butanone). A similar effect may have been observed by Hulett [20] in the first-order bromination of di-isopropyl ketone, where it was possibly found that the second bromine entered the molecule more slowly than the first one, and by Bell and co-workers [15] in the zero-order bromination of diethyl ketone for which the kinetics were zero-order for only 20 % of reaction (hydroxide catalysis in both studies).

In 3-methyl-3-chloro-2-butanone (the result of substituting two methyl groups α to chlorine in chloroacetone), the rate of H – D exchange at the α′-methyl group is slower than for any of the other chloro-ketones studied. This may be understood in terms of steric compression in the transition state arising from the increased bulkiness of the ketone (possibly an entropy effect). An alternative explanation based on the degree of hyperconjugative interaction in an enol(ate)-like transition state is not consistent with the other data.

Certain reservations must be made regarding the foregoing analysis. While we have made only measurements on chloroketones, the discussion has been in terms of haloketones and halogenation in general. One should expect different behaviour among the different halogens, chlorine, bromine, and iodine, but it is difficult to predict what this behaviour will be; particularly in cases such as 2-butanone. Bromo- and iodo-substituted ketones would be expected to be more acidic than the respective chloroketones on the basis of the polarizabilities and inductive effects of these halogens,

$$I > Br > Cl$$

however, the increase in the bulk and steric hindrance from substitution of these halogens in a ketone will be, to judge from the results of this investigation, of major importance in some cases. From this point of view, a study of rates of exchange in bromo- and iodoketones would be desirable, but elimination of competing side reactions and the problem of the solubilities of these ketones in a suitable deuterium pool seem insurmountable. A second reservation concerns the contribution of possible acid-catalysis to the observed pseudo first-order rate constants. Since chloroacetone has been shown to exhibit primarily general base-catalyzed proton exchange down to relatively low pH values (< 2.7),[2] we have not investigated the magnitudes of the catalytic constants for the acid species in solution, D_3O^+ and CD_3COOD. Rates of exchange at the unchlorinated aliphatic groups, however, may

exhibit acid-catalysis at the pD (= 3 – 4) necessary to meet solubility requirements in this study. In an investigation of H – D exchange in 2-butanone, Rappe [21] has found the rate ratio for exchange at the methyl and methylene groups to be a measure of the contribution of acid-catalysis and, in a buffer solution of composition similar to that used in this study, reports an orientation of exchange that indicates primarily basic catalysis. However, uncertainty remains, and a detailed investigation will be necessary to test this point.

C. Favorskii rearrangement. α-Haloketones with exchangeable protons at the α′-position are known to undergo the Favorskii rearrangement in the presence of base.[22] No Favorskii product was detectable on the time scale

Table 2. S_N2 Displacement of chlorine by acetate at 42°C.

Ketone	Initial concentrations Ketone M	Acetate M	$k \times 10^6$ (l mol^{-1} sec^{-1})
Chloroacetone	1.08	1.08	1.4
1-Chloro-2-butanone	1.25	1.04	1.3
3-Chloro-2-butanone	1.06	1.06	0.7

of the S_N2 and exchange reactions indicating that this reaction is slower by at least a factor of 10 than the slowest rates of exchange for the chloroketones studied in this acetate buffer. Proton exchange prior to rearrangement has been observed previously.[23,24] A detailed discussion of pre-equilibria in the Favorskii rearrangement of branched and unbranched monochloroketones is to be found elsewhere.[25]

EXPERIMENTAL

Measurements were made with a Varian A-60 NMR spectrometer. Gas chromatography on a preparative scale was carried out on a Perkin-Elmer F 21 gaschromatograph. A Pye Unicam model 84 gaschromatograph was used for analysis of the starting ketones.

Preparation and materials. Dr. L. Knutsson of these laboratories kindly provided chromatographically pure samples of chloroacetone, 1,1-dichloroacetone, and 3-chloro-2-butanone. 1-Chloro-2-butanone and 3-methyl-3-chloro-2-butanone were available from previous work in these laboratories, and were purified by preparative VPC on a 2.7 m column (20 % polyethyleneglycol 1500 och Chromosorb A 45/60). Analyses on a 1.5 m column (10 % polyethyleneglycol 20 M on 100 – 120 Mesh Diatomite C) showed only single component samples (pen deflection 50 % of scale for the main component).

Two buffer solutions were prepared. The exchange studies were carried out in a solution prepared by weight and volume (0.948 g CD_3COONa, 4.111 g D_2O, 6.639 g CD_3COOD; 10 ml total volume) which is 1.12 M in acetate. The solution for the study of side reactions was prepared in the same manner (6.693 g $CH_3COONa.3H_2O$, 7.954 g H_2O, 13.401 g CH_3COOH; 25 ml total volume) and is 1.19 M in acetate. The isotopic purity of the buffer for the exchange studies was checked in the NMR and was found to contain approximately 4 % ^1H based on the total available exchangeable protons and deuterons.

Exchange kinetics. A typical run is described: 0.5 ml of catalyst was pipetted into an NMR tube, which was then brought to 42.20 ± 0.01°C in a thermostated oil bath. 0.07 ml of ketone was added from an Agla micrometer syringe (Burroughs Wellcome and Co., London), the contents of the tube rapidly mixed by shaking, and the time recorded. For exchange in 1,1-dichloroacetone, the tube was kept in the probe (41 ± 2°C) between measurements. Exchange in the other ketones was slow enough, so that the NMR-tube could be transferred to a thermostated bath between measurements.

Integrals were multiply recorded over reacting peaks and an internal reference. In cases where no internal reference was available, the sum of the integrals over the reacting peaks and the DDH peak was observed to remain constant (with small statistical variation) and was therefore used in place of an internal reference. The integral values were treated according to the equation

$$\ln\left\{\frac{H_0^{CH_n}-H_\infty^{CH_n}}{H^{CH_n}-H_\infty^{CH_n}}\right\}=\frac{[BD]_0+[BH]_0+n[CH_n]_0}{[BD]_0+[BH]_0}\,kt \qquad (3)$$

assuming the complete absence of all isotope effects.[18] The 0 and ∞ subscripts refer to initial and equilibrium values, respectively. H^{CH_n} is the integrated intensity of the proton signal of CH_n in the NMR, and $[BH]_0$ and $[BD]_0$ the initial proton and deuteron content in mol/l of the solvent. Eqn. (3) is an approximation for the case when there are two exchanging groups in the same molecule, and applies when $[BD]_0$ is much greater than the total proton content of the solution. $H_\infty^{CH_n}$ was calculated from the relation [18]

$$H_\infty = H_0\,\frac{[BH]_0+n[CH_n]_0+m[CH_m]_0}{[BD]_0+[BH]_0+n[CH_n]_0+m[CH_m]_0} \qquad (4)$$

assuming no equilibrium isotope effects, since the experimental values were considered unreliable due to the competing S_N2 side reaction. In ketones where one group exchanged nearly to completion before measureable exchange occurred at the other position, slight variations in the *r.h.s.* of eqn. (4) were necessary to evaluate k.

The presence of hydrated ketone was not detectable for any of the chloroketones. This is somewhat puzzling, since chloroacetone is known to be 38 % hydrated in dilute aqueous solution [26] at an equilibrium which is rapidly achieved. However, it is well known that in sufficiently acid (and presumably basic) solutions, the hydration equilibrium is so rapid, that only a single average signal of the two forms appears in the NMR.[26]

S_N2 Kinetics. By assuming volume additivity and using tabulated values for the densities of chloroacetone and 3-chloro-2-butanone, the volume of ketone to be added to 0.5 ml of buffer 1.19 M in acetate to give a ketone concentration equal to the acetate concentration could be calculated. Thus eqn. (2) could be used to analyse the kinetics. In the case of 1-chloro-2-butanone, eqn. (1) was used.

Integrals were multiply recorded over the CH_2Cl-peak or the CH_3-peak. The acetic acid CH_3-peak at reduced spectrum amplitude served as an internal reference.

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