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Alternative Routes in Hydroxide Ion-catalyzed Hydrogen Isotope Exchange of Unsymmetrical Ketones

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The hydroxide ion-catalyzed detritiation of a number of unsymmetrical ketones has been studied in water at 298.15 K. The hydrogen isotope exchange takes place in the α-positions. The rate coefficients for both of these parallel reactions have been calculated. On the basis of these kinetic results the contributions of alternative routes in different base-catalyzed reactions of ketones can be estimated.

Base-catalyzed reactions of ketones has been the subject of numerous kinetic studies.[1,2] Especially halogenation, deuteriation, and racemisation reactions have been thoroughly studied. It has been suggested that in all of these cases the proton abstraction from the ketone is the rate-limiting step of the reaction.[1,2] Although an alternative rate-limiting step has been proposed for the halogenation of some aliphatic ketones,[3] a recent study[4] reveals that this assumption is less probable. Only little information is available on the relative reactivities of alternative acidic sites. The base-catalyzed deuteriation of unsymmetrical ketones has previously been studied[5] but most of these papers concern only the deuteriation of 2-butanone.[5a,b,f,g,i] In addition the accuracy which has been obtained by the NMR method is insufficient for detailed studies. Partly this is due to secondary isotope effects which lead to deviations from the first-order kinetics. A more exact information on the relative reactivities of the alternative acidic sites is, however, important. Therefore the detritiation of unsymmetrical ketones $-CH_2COCH_3$ and $>CHCOCH_3$ was subjected to a thorough kinetic study.

EXPERIMENTAL

Labeling. Most of the ketones used in the kinetic measurements were products of Fluka AG; 1-phenyl-1-buten-3-one was purchased from British Drug House. The ethyl *tert*-butyl ketone used in the kinetic measurements was prepared by Taskinen.[6] 1-Methoxy-2-propanone was synthesized by the following method:[7] A solution of 225 g of concentrated sulfuric acid in 58 g of water was dropped into a solution of 188 g of sodium dichromate and 101 g of 1-methoxy-2-propanol in 100 cm³ of water during 6 h with vigorous stirring. During the addition the temperature of the reaction mixture was kept at 293 – 298 K. Leaving the solution overnight the ketone was extracted into diethyl ether. The ethereal solution was dried with potassium carbonate, the ether removed in vacuum and the ketone purified by distillation. B.p. 387 – 388 K. ^{1}H NMR δ 3.80 (2 H), 3.35 (3 H), 2.05 (3 H).

In the tritium labeling 10 cm³ of a ketone was stirred with 30 cm³ of 0.1 mol dm^{-3} sodium hydroxide and about 1 mm³ of tritiated water at room temperature from 20 to 50 h depending on the substrate. The activity of the tritiated water (The Radiochemical Centre) was 10^7 s^{-1} mm^{-3}. In most cases the aqueous solution and the ketone were immiscible and therefore the reaction mixture was shaken vigorously to emulsify the two phases and thus increase the rate of isotope exchange reaction. After labeling the ketone was extracted into diethyl ether with three portions of 20 cm³. The efficiency of the extraction was increased by salting out the ketone from the aqueous solution with sodium chloride. The ethereal solutions were dried over magnesium sulfate, the ether removed in vacuum and the ketone distilled. The purity of the product was controlled by NMR spectroscopy. The extent of labeling was studied with a Wallac 8100 scintillation counter and 1 mm³ samples from the various ketones were found to give activities between 200 and 2000 s^{-1}. In the tritiation of 1-phenyl-1-buten-3-one the

above-mentioned procedure was slightly modified: The solid ketone (10 g) was dissolved in 10 cm³ of diethyl ether and the solution was stirred vigorously with 30 cm³ of 0.1 mol dm⁻³ sodium hydroxide and 2 mm³ of tritiated water for 80 h at room temperature. The ketone was extracted into diethyl ether with three portions of 20 cm³ and the ethereal solution was dried over magnesium sulfate. After the ether had been evaporated the ketone was crystallized from benzine. In some cases the labeling was performed in dimethyl sulfoxide–water mixtures ($x_{DMSO} = 0.8 - 0.9$) with tetramethylammonium hydroxide (0.01 mol dm⁻³) as catalyst. Under these conditions the labeling takes place in one phase and, additionally, the relatively high basicity of this medium [8] favors the hydrogen isotope exchange reaction. After tritiation the labeled product was extracted into pentane and distilled.

Kinetic measurements. Kinetic measurements were performed in water at 298.15 ± 0.05 K with 0.1 mol cm⁻³ sodium hydroxide as the catalyst. 85 cm³ of the sodium hydroxide solution was thermostated to the desired temperature and 0.04–0.2 cm³ of the labeled substrate was added. After vigorous shaking the first sample was taken with a 5 cm³ semi-automatic pipet. The content of the pipet was added to 2 cm³ of 0.3 mol dm⁻³ sulfuric acid to stop the reaction. The solution was saturated with disodium hydrogen phosphate and the ketone was extracted into 10 cm³ of anisole. The 5 cm³ samples taken from the organic layer were transferred to the vials of a scintillation counter with 10 cm³ of the scintillation liquid (10 g of diphenyloxazole and 0.25 g of *p*-bis(*o*-methylstyryl)benzene in 2.5 dm³ of toluene). The decrease in the activity of the ketone was followed with the Wallac 8100 scintillation counter. 10 to 15 samples were withdrawn from each kinetic run. The final samples were taken after ten half lives. The first-order rate coefficients were calculated from eqn. (1)

$$k = \frac{1}{t} \ln \frac{N_0 - N_\infty}{N_t - N_\infty} \qquad (1)$$

where t denotes the time calculated from the withdrawal of the first sample and N_0, N_t, and N_∞ are the measured count rates for the first sample, for the sample taken at time t, and for the final sample, respectively. In most cases the ketone contained, however, alternative exchangeable α-hydrogens and therefore the above-mentioned procedure was slightly modified. The labeled substrate (0.1–0.2 cm³) was added to 180 cm³ of 0.1 mol dm⁻³ aqueous sodium hydroxide and first 4–5 samples were withdrawn as fast as possible in order to extrapolate the count rates to the beginning of the reaction. During the progress of the reaction about 30 samples were withdrawn. The first-order rate coefficients, k_a and k_b, for the parallel reactions were calculated by eqn. (2) on a Univac 1108 computer using

$$\frac{N_0 - N_t}{N_0 - N_\infty} = x_a(1 - e^{-k_a t}) + (1 - x_a)(1 - e^{-k_b t}) \qquad (2)$$

the method of least squares.[9] In eqn. (2) x_a denotes the mol fraction of tritium in the more acidic site of the ketone, k_a the first-order rate coefficient for the detritiation of the more acidic α-hydrogen and k_b the corresponding rate coefficient for the detritiation of the less acidic α-hydrogen. Notations N are as in eqn. (1) except N_0 which is the extrapolated count rate at the beginning of the reaction.

RESULTS AND DISCUSSION

On the basis of the present kinetic data the fraction of tritium in the alternative acidic sites of the labeled ketones was calculated and the results are collected in Table 1. It can be concluded that the x_a-values (mol fraction of tritium in the more acidic α-hydrogen) give in most cases the fractions of tritium in the methyl group. Only the phenyl and the methoxy group in compounds 10 and 12 are more electronegative than are the hydrogen atoms in the methyl group. It is thus reasonable to assume that only in these two cases the methylene hydrogens are more acidic than those in the alternative methyl group. Qualitative evidence for this assumption can be obtained by studying the alternative hydrogen exchange reaction, the deuteriation of ketones. The results from these measurements really reveal that only for compounds 10 and 12 the deuteriation of the methyl group takes place with a slower rate than that of the methylene group. If the tritiation of unsymmetrical ketones had led to an equilibrium roughly a statistical distribution between the alternative α-hydrogens is to be expected. For compounds 2, 4, 5, 6, and 7 the x_a-values in Table 1 are really seen to be in accordance with the statistical values 0.75 or 0.60 with in the limits of experimental errors. For compounds 3, 9, 10, and 12 the measured x_a-values are slightly higher than can be expected on the basis of the amount of exchangeable hydrogen atoms, but the distribution of tritium is, however, in favor of the more acidic site of the substrate as a result of kinetic control. With the exception of compounds 5 and 6 the conformity

Table 1. Detritiation of unsymmetrical ketones $RCOCH_3$ in 0.1 mol dm^{-3} aqueous sodium hydroxide at 298.15 K.

No.	$RCOCH_3$ R	x_a [a]	$k_a/10^{-4}$ s^{-1} [b]	$k_b/10^{-4}$ s^{-1} [c]
1	$(CH_3)_3C$	–	0.961	–
		–	0.972	–
2	$(CH_3)_2CH$	0.664	1.88	0.250
		0.735	1.73	0.159
		0.703	1.78	0.175
3	$(CH_3)_3CCH_2$	0.724	2.29	0.989
		0.797	2.19	0.841
4	$CH_3(CH_2)_3$	0.600	1.58	1.14
		0.600	1.63	1.09
5	$(CH_3)_2CHCH_2$	0.722	1.87	0.633
		0.570	2.20	0.857
6	$CH_3(CH_2)_2$	0.667	1.59	0.957
		0.524	1.74	1.034
7	CH_3CH_2	0.600	1.52	1.18
		0.600	1.38	1.38
8	CH_3	–	2.19	–
9	$Ph-CH_2CH_2$	0.743	3.58	2.04
		0.785	3.41	1.99
		0.675	3.65	2.15
10	$Ph\text{-}CH_2$	0.570	81.6	3.85
		0.574	85.1	3.91
11	$Ph\text{-}CH=CH$	– [d]	3.58	–
		–	3.53	–
12	CH_3OCH_2	0.463	8.74	5.45
		0.477	9.00	5.60
13	Ph	–	5.75	–
		–	5.72	–

[a] x_a = mol fraction of tritium in the more acidic site of the substrate. [b] k_a = first-order rate coefficient for the detritiation from the more acidic site of the substrate. [c] k_b = first-order rate coefficient for the detritiation from the less acidic site of the substrate. [d] The isotope exchange in the CH-group was negligible in the used conditions.

Table 2. Second-order rate coefficients for the detritiation of ketones $RCOCH^*_3$ at 298 K.

No.	$RCOCH_3$ R	σ^*_R	$k_{CH_3}/10^{-3}$ mol^{-1} dm^3 s^{-1}
1	$(CH_3)_3C$	−0.320	0.966
2	$(CH_3)_2CH$	−0.200	1.80
3	$(CH_3)_3CCH_2$	−0.140	2.24
4	$CH_3(CH_2)_3$	−0.130	1.61
5	$(CH_3)_2CHCH_2$	−0.125	2.03
6	$CH_3(CH_2)_2$	−0.115	1.70
7	CH_3CH_2	−0.100	1.45
8	CH_3	0.000	2.19
9	$Ph-CH_2CH_2$	+0.080	3.54
10	$Ph-CH_2$	+0.225	3.87
11	$Ph-CH=CH$	+0.410	3.55
12	CH_3OCH_2	+0.520	5.52
13	Ph	+0.600	5.73

of the parallel x_a-values is seen to be satisfactory, since the evaluation of the three parameters from a single run requires high accuracy in the kinetic experiments. The best results were obtained when the rate coefficients for parallel reactions differ substantially as shown in previous studies [7] for the detritiation of methyl benzyl ketone (compound 10).

As discussed above the faster of the alternative detritiation reactions is that of the methyl group with exception of compounds 10 and 12, in which the methylene hydrogens are more acidic. The accuracy of the measured k_a-values is seen to be satisfactory, since the difference between the parallel k_a-values is less than ten per cent with exception of compound 5. Also the parallel k_b-values are seen to be almost equal with the exception of compounds 2, 3, and 5. In the case of acetophenone the present kinetic data can be compared with the results in previous studies. The second-order rate coefficient, 0.00574 mol^{-1} dm^3 s^{-1}, calculated from the first-order rate coefficients in Table 1 is in good agreement with the values of 0.0058 mol^{-1} dm^3 s^{-1} (Ref. 10) and 0.0054 mol^{-1} dm^3 s^{-1} (Ref. 11).

Detritiation of the methyl group. On the basis of the present kinetic data structural effects in reaction (3), in which the detritiation takes

$$RCOCH^*_3 \xrightarrow{OH^-} RCOCH_3 \qquad (3)$$

place from the methyl group of an unsymmetrical ketone, can be discussed. The second-order rate coefficients k_{CH_3} (Table 2) for this reaction were calculated from the k_a-values in Table 1 by dividing the first-order rate coefficients with the hydroxide ion concentration. As discussed above in the case of compounds 10 and 12 the k_{CH_3}-values must be calculated from the first-order rate coefficients k_b in Table 1. When the logarithms of the rate coefficients k_{CH_3} are plotted against the σ^*-values [12] of the α-substituent a linear correlation is observed (Fig. 1). When the slope of this plot was calculated by the method of least squares the kinetic data for the detritiation of the phenyl and styryl substituted derivatives (compounds 11 and 13) were neglected since resonance effects may be operative in these reactions. From the kinetic data for eleven ketones the relationship (4)

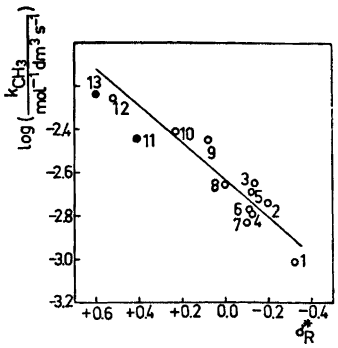
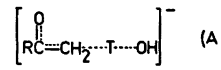


Fig. 1. Plot of the logarithms of rate coefficients of detritiation for $RCOCH_3$ against substituent constant σ^*_R. The numbers of the compounds refer to Table 2. Compounds 11 and 13 (filled circles) were neglected when the correlation line was plotted.

was obtained. The rate coefficients for the detritiation reactions of the phenyl and styryl

$$\log k_{CH_3} = (0.862 \pm 0.117)\sigma^*_R - (2.639 \pm 0.026) \quad (4)$$

substituted derivatives are seen to differ only slightly from the linear free energy correlation; this reflects that the stabilization due to the conjugation of the carbonyl group and the



aromatic ring (R = phenyl in scheme A) has diminished only slightly in the attainment of the transition state A of reaction (3).

Detritiation of the methylene group. On the basis of the present kinetic data structural effects in the detritiation of the methylene hydrogens can be discussed. In the case of compounds 3 – 10 and 12 in Table 1 detritiation from the methyl and methylene group are parallel reactions and as mentioned above the lower of the measured rate coefficients is that of the detritiation of the methylene group except for compounds 10 and 12. The second-order rate coefficients for reaction (5) are collected in Table 3. When the logarithms of these

$$R'CH^*_2COCH_3 \xrightarrow{OH^-} R'CH_2COCH_3 \qquad (5)$$

rate coefficients are plotted against the σ^*-values of the substituents attached at the methylene

Table 3. Second-order rate coefficients for the detritiation of ketones R'CH*$_2$COCH$_3$ at 298 K.

No.	R'CH$_2$COCH$_3$ R'	$\sigma^*_{R'}$	$k_{CH_3}/10^{-3}$ mol^{-1} dm^3 s^{-1}
3	$(CH_3)_2C$	−0.320	0.914
4	$CH_3(CH_2)_2$	−0.115	1.11
5	$(CH_3)_2CH$	−0.200	0.745
6	CH_3CH_2	−0.100	0.996
7	CH_3	0.000	1.28
8	H	+0.490	2.19
9	Ph-CH_2	+0.225	2.06
10	Ph	+0.600	83.3
12	CH_3O	+1.46	8.87

group (Fig. 2) a linear correlation is observed when the phenyl substituted derivative is excluded. The slope of this plot was calculated from the kinetic data by the method of least squares (eqn. 6). Although only inductive polar effects are seen to be operative in the detritia-

$$\log k_{CH_3} = (0.588 \pm 0.043)\sigma^*_{R'} - (2.908 \pm 0.024) \quad (6)$$

tion of the above-mentioned compounds resonance effects cannot be excluded. It can be seen (Fig. 2) that the phenyl substituted derivative reacts with a rate which is markedly higher (by a factor of about 30) than might be expected on the basis of inductive polar effects only. The accelerating effect of this substituent must be due to resonance effects since in the transition state (B) the phenyl

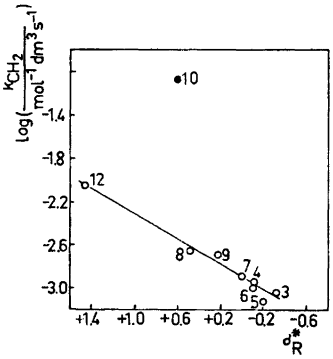
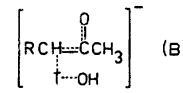


Fig. 2. Plot of the logarithms of rate coefficients in detritiation of R'CH$_2$COCH$_3$ against substituent constants $\sigma^*_{R'}$. The numbers refer to Table 3. Compound 10 (filled circle) was neglected when the correlation line was plotted.



(B)

group (R' = phenyl) is in conjugation with the partial double bond system.

On the basis of the obtained linear free energy correlations (4) and (6) rate coefficients for the detritiation of α-methyl and α-methylene hydrogens in different unsymmetrical ketones can be estimated. The measured rate coefficients can also be applied in the determination of the pK_a-values of different acidic sites of ketones.[13]

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