66. *The Bromination of Di-isopropyl Ketone in Alkaline Solution.*

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Measurements have been made on the rate of bromination of di-isopropyl ketone in alkaline solution, under conditions which lead to pseudo first-order kinetics. The reaction has been studied in the temperature range 0 to 50°. The Arrhenius plot exhibits marked curvature below 20°. The most probable reason for this curvature is quantum mechanical leakage of protons through the energy barrier. The results are fitted to Bell's equations for a parabolic barrier, and the significance of the barrier dimensions is discussed.

In a recent Paper it was reported that the Arrhenius plot for the fluoride ion-catalysed bromination of ethyl 2-oxocyclopentanecarboxylate exhibited marked curvature at temperatures below $-10°$.[1] This deviation was explained in terms of the so-called tunnel effect.[2] The hydrogen isotope effect in this reaction was consistent with this explanation.[3,4] A similar reason has been advanced for the curvature of the Arrhenius plots observed in the region of $-100°$ in some proton-transfer reactions involving the trinitrobenzyl ion.[5,6]

It was hoped that by using substrates of a ketonic nature rather than a carbanion structure, further evidence of tunnelling might be found at temperatures not too far below room temperature. Di-isopropyl ketone was chosen because it has only one hydrogen atom attached to the carbon atoms adjacent to the carbonyl group. If the hydrogen isotope effect on the reactions of this ketone is investigated, there will be no complications due to secondary isotope effects from other hydrogen or deuterium atoms on the same carbon atom. Secondary effects due to replacement of hydrogen by deuterium on the carbon atom on the opposite side of the carbonyl group are expected to be small. The transfer of a proton from a simple ketone to a base does not occur readily, and so a strong base is required. The base used in this study is the hydroxide ion.

Experimental

Materials.—The di-isopropyl ketone was a B.D.H. sample. It was distilled in an all-glass apparatus, and then fractionated through a 45 × 1·7 cm. column packed with $\frac{1}{16}$ in. Dixon

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[1] Hulett, *Proc. Roy. Soc.*, 1959, *A*, **251**, 274.
[2] Bell, *Trans. Faraday Soc.*, 1959, **55**, 1.
[3] Bell, Fendley, and Hulett, *Proc. Roy. Soc.*, 1956, *A*, **235**, 453.
[4] Hulett, *J.*, 1960, 468.
[5] Caldin and Harbron, *J.*, 1962, 3454.
[6] Caldin and Kasparian, to be published.

stainless steel gauze rings. The column was vacuum jacketed and electrically heated. Fractions were taken every 0·1° between 123·6 and 124·4° and analysed on a gas chromatograph. The higher-boiling fractions proved to be the pure ketone.

All other chemicals were AnalaR samples.

Sodium hydroxide solutions were made up with boiled out distilled water and kept under carbon dioxide-free conditions.

Method.—A known weight of di-isopropyl ketone was dissolved in water to give a solution about 0·4M. About 0·5 ml. of this solution was added by means of an automatic pipette to each of eleven tubes containing 2 ml. of a solution of bromine in excess of alkali, and kept in the thermostat bath. The reaction was stopped in successive tubes at various time intervals by acidification, immediately followed by addition of excess potassium iodide solution. The iodine liberated was titrated against standard thiosulphate, to give the amount of bromine remaining unreacted. A twelfth tube, not containing ketone, was treated similarly to estimate the initial bromine concentration. These experiments enabled the hydroxide ion concentration and, from the stoicheiometry of the reaction, the rate of disappearance of the unbrominated ketone, to be calculated.

The concentration of the ketone used was only about 5% of that of the hydroxide ion. The maximum conversion used corresponded to the monobromination of not more than 50% of the ketone. The hydroxide-ion concentration was thus effectively constant during each run, and the results were therefore analysed on the basis of pseudo first-order kinetics. The good straight lines obtained justified this procedure.

A preliminary test indicated that the freshly distilled ketone did not liberate iodine from potassium iodide, so that the full titre is due to unchanged bromine.

The reaction was investigated at 5° intervals over the temperature range 0 to 50°. Above 10° a conventional water thermostat was used, controlled to ±0·02°. Below 10° a low-temperature bath, accurate to ±0·05°, was used.[1]

Stoicheiometry of the Reaction.—The stoicheiometry of the reaction has not been investigated in detail in this study. It was hoped that the ketone concentration in solution could be checked by determining the quantity of bromine required for complete bromination. The ketone was left with bromine in alkaline solution at room temperature for about 18 hr. It was found that *ca.* 1·5 atoms of bromine per mole of ketone had been taken up. Further uptake of bromine occurred, but very slowly. After 65 hr. slightly over 2 atoms of bromine per mole of ketone had been used. This method of analysis for the ketone was clearly unsatisfactory.

This experiment established that the uptake of one atom of bromine per mole of ketone occurs quite readily. This could take place according to the equation:

$$\mathrm{Me_2CH{\cdot}CO{\cdot}CHMe_2 + OBr^- \longrightarrow Me_2CBr{\cdot}CO{\cdot}CHMe_2 + OH^-} \qquad (1)$$

The monobromo-ketone, however, would be expected to be at least as reactive as, if not more reactive than, the original substrate. Yet the evidence is that further bromination takes place more slowly. Probably the monobromo-ketone exists in solution almost entirely in the hydrated form $\mathrm{Me_2CBr{\cdot}C(OH)_2{\cdot}CHMe_2}$, or, in strongly alkaline media, as $\mathrm{Me_2CBr{\cdot}CO^-(OH){\cdot}CHMe_2}$. Neither of these forms would be reactive, and so further bromination to yield the dibromo-ketone does not occur.[7]

The results presented here confirm those of Cullis and Hashmi on the halogenation of this ketone.[8] They found that the limiting consumption of hypobromite ion is two ions per mole of ketone. The main products which they identified were monobromoisobutyric acid and propan-2-ol. The second stage of the bromination would thus appear to be

$$\mathrm{Me_2CBr{\cdot}CO{\cdot}CHMe_2 + OBr^- + OH^- \longrightarrow Me_2CBr{\cdot}CO_2^- + Me_2CH{\cdot}OH + H_2O + Br^-} \qquad (2)$$

According to Cullis and Hashmi, this reaction does not go quite to completion. (The analogous iodination appears to reach equilibrium when the second stage is only about 50% complete.[9]) The small amount of reaction beyond this which has been noted in this study may be due to slow oxidation or bromination of the propan-2-ol in the strong alkaline solutions used. However, the evidence is not conclusive as loss of bromine may have occurred during the very long period allowed for the reaction.

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[7] Bell, personal communication.
[8] Cullis and Hashmi, *J.*, 1957, 3080.
[9] Cullis and Hashmi, *J.*, 1957, 1548.

The process is thus far from simple. Despite these complications, however, it appears that under the conditions used in the present study simple monobromination is occurring, and the results have been analysed in terms of reaction (1) alone.

The rate of reaction is quite slow, even in 0·16N-sodium hydroxide. The rate with weaker bases would be even slower. In particular, water, although present in large concentrations, is such a weak base that the contribution of solvent catalysis to the total rate may be ignored. This is found to be so in the analogous reaction of acetone.[10]

RESULTS

The observations were treated as simple first-order reactions. In each case good straight lines were obtained which cut the zero time axis at a point corresponding to a little less ketone than was weighed out. The only inactive impurity likely to be present in the ketone is water, but the quantity should not be large. Alternatively this discrepancy may be due to the more rapid reaction of a small proportion of a more active material such as the enol form of the ketone. The proportion of enol form present at equilibrium is not known, but it may well be a few percent in strongly alkaline media. Occasionally the first point on the graph also lay slightly above the straight line through the remaining points.

The collected results are shown in Table 2 and in the Figure. The first Arrhenius equation shown at the head of the Table is based on the six points at high temperatures where the curve is linear. Rate constants derived from this equation, which corresponds to the full line in the Figure, are shown in the column headed $k_{\text{Arrh.}}$. The differences between $k_{\text{obs.}}$ and $k_{\text{Arrh.}}$ give a measure of the curvature of the plot. At the lowest temperature, the divergence is about 30% of $k_{\text{Arrh.}}$, or some fifteen times the experimental error. This suggests that the effect is real. The apparent activation energy falls from 14·1 kcal. mole^{-1} above 25° to about 12·1 kcal. mole^{-1} at 5°.

TABLE 1.

Details of a typical experiment.

Bromination of di-isopropyl ketone at −0·2°.

a = Initial concentration of ketone (by weighing) = 8·00 × 10^{-3}M.
a' = Initial concentration of ketone (by extrapolation) = 7·57 × 10^{-3}M.
x = Concentration of ketone used after time t.
b = Concentration of hydroxide ion = 1·680 × 10^{-1}M.

t (min.)	10	22	35	55	75	101	133	157	178	194	230
$(a - x) \times 10^3$ (obs.)	7·49	7·13	6·87	6·52	6·24	5·86	5·43	5·17	4·83	4·68	4·32
$(a' - x) \times 10^3$ (calc.)	7·38	7·16	6·93	6·59	6·28	5·88	5·43	5·12	4·86	4·67	4·27

The gradient of the straight line obtained by plotting $\log_{10}(a - x)$ against t is $-60\,bk/2{\cdot}303$. whence $k = 2{\cdot}47 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

TABLE 2.

Temperature dependence of reaction rate.

$k_{\text{Arrh.}} = 3{\cdot}76 \times 10^7 \exp(-14110/\boldsymbol{R}T)$; $k'_{\text{Arrh.}} = 6{\cdot}58 \times 10^6 \exp(-13030/\boldsymbol{R}T)$.

Temp. (°c)	No. of runs	$10^4k_{\text{obs.}}$	$10^4k_{\text{Arrh.}}$	$10^4k'_{\text{Arrh.}}$	10^4k_q
−0·2	4	2·47 ± 0·05	1·89	2·38	2·54
5·0	4	3·77 ± 0·04	3·05	3·74	3·78
10·0	4	5·69 ± 0·07	4·84	5·68	5·50
15·0	5	8·37 ± 0·11	7·47	8·49	7·96
20·0	3	12·1 ± 0·11	11·4	12·5	11·6
25·0	4	16·7 ± 0·3	17·1	18·2	16·9
30·0	3	25·6 ± 0·2	25·3	26·2	24·8
35·0	3	36·7 ± 0·15	37·0	37·2	36·0
40·0	3	54·7 ± 0·9	53·8	52·3	52·1
45·0	4	73·7 ± 0·5	76·4	72·2	75·0
50·0	6	107·8 ± 2·0	107·9	100·1	107·4

Alternatively, the data can be examined in terms of a forced fit to an Arrhenius equation over the whole temperature range. This has been done by the method of least squares, giving the second equation at the head of the Table. The rate constants derived from this equation are tabulated as $k'_{\text{Arrh.}}$. There is a systematic divergence between the values so calculated and

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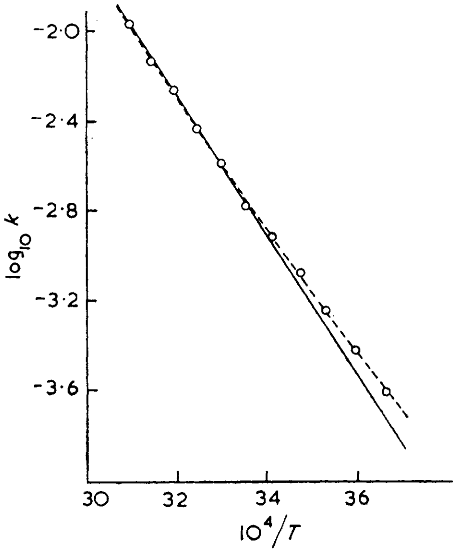
[10] Bell and Longuet-Higgins, *J.*, 1946, 636.

the observed rate constants, corresponding to the curvature of the plot. At the centre and high-temperature end of the line the discrepancies are 9 and 8%, respectively, that is, some six times the experimental error. This Arrhenius equation, with an apparent activation energy of 13·03 kcal. mole^{-1}, is thus not a satisfactory fit to the data.

The significance of k_q will be discussed later.



—— $\log_{10} k_{\text{Arrh.}}$. - - - - $\log_{10} k_q$.

DISCUSSION

Curved Arrhenius plots may arise from a number of causes.[11]

An obvious possibility is that the reaction may proceed by alternative routes. That with the greater activation energy will be more important at high temperature and *vice versa*. In this case, the two processes would have the same rates at about 20°. This phenomenon is observed occasionally,[12, 13] but has not been noted in any simple proton-transfer reaction. It would not be easy to conceive of two such steps which might govern the present reaction. Thus, while not being entirely excluded, this explanation for the observed curvature is unlikely.

Another possible explanation lies in the variation of the enthalpy of activation with temperature. Many results have been analysed in terms of the equation

$$\log_e k = -A/T + B \log_e T + C$$

which implies that $\Delta H^\ddagger$ is a linear function of temperature and $\Delta C_p^\ddagger$ is constant. The most important factor governing $\Delta C_p^\ddagger$ is the change in solvation on formation of the transition state.[14] The curvature observed in the present reaction would correspond to $\Delta C_p^\ddagger$ about +145 cal. mole^{-1} deg.$^{-1}$. In nearly every case where $\Delta C_p^\ddagger$ has been significant, its sign is negative—these reactions have involved the interaction of neutral species. Processes such as the hydrolysis of halides by hydroxide ion, in which $\Delta C_p^\ddagger$ might be positive, have shown no deviation from the Arrhenius equation.[15] This reaction would thus be exceptional if the very marked deviation were due to this cause. $\Delta S^\ddagger$ calculated from the results at high temperature is about −26 cal. deg.$^{-1}$ mole^{-1}. This entropy decrease on activation suggests a greater degree of order in the transition state than in the reactants, and so would lead to a curvature in the opposite direction to that observed.

[11] Hulett, *Quart. Rev.*, 1964, **18**, 227.

[12] Billinge and Gowenlock, *Proc. Chem. Soc.*, 1962, 24.

[13] Ashmore and Burnett, *Trans. Faraday Soc.*, 1962, **58**, 1801.

[14] Moelwyn-Hughes, *J.*, 1961, 1517.

[15] Fells and Moelwyn-Hughes, *J.*, 1957, 398.

Variation of solvent structure with temperature may lead to curvature of the Arrhenius plot.[1] This would, however, lead to a deviation in the opposite direction to that observed,[1,5] unless there is a specific effect due to interaction of the hydroxide ion with the solvent. If such a specific effect existed it should be noticed in all reactions involving the hydroxide ion in aqueous solution in this temperature range. This does not occur.[15]

Curved Arrhenius plots are expected for simple proton-transfer reactions if there is quantum mechanical leakage of protons through the energy barrier opposing the reaction.[16] This curvature would be in the direction observed. Bell's treatment for a one-dimensional parabolic barrier [2] has been applied to the present results, with the quantum correction

$$Q = \frac{\pi\alpha/\beta}{\sin \pi\alpha/\beta} - \frac{\alpha \exp(\alpha - \beta)}{\beta - \alpha}$$

where $\alpha = E^*/kT$ and $\beta = 2\pi^2 a(2mE^*)^{\frac{1}{2}}/h$. E^* is the height of the energy barrier the width of which is $2a$. Values of E^* and a were obtained by a method of trial and error to give the best fit to the experimental results. The final values chosen were $E^* = 17{\cdot}8$ kcal. mole^{-1} and $a = 0{\cdot}563$ Å. The fit of the curve is very sensitive to the value of a chosen, being significantly worse when $a = 0{\cdot}565$ Å. The results of this calculation are shown as k_q in Table 2 and as the dotted locus in the Figure. The discrepancies between k_q and $k_{obs.}$ are random, and only about twice the average experimental error. In view of the approximate model used, this agreement is adequate. The agreement between k_q and $k_{obs.}$ is very much better than that between $k'_{Arrh.}$ and $k_{obs.}$. It seems, therefore, to be a reasonable hypothesis that this curvature is most probably due to non-classical proton transfer.

Barrier Dimensions.—(*a*) *Height.* In the calculations it has been assumed that the observed activation energy depends only upon the energy required to move the proton, other contributions [17] being neglected. Repulsion and electrostatic effects involving a neutral substrate may be small, but the large $\Delta S^‡$ suggests that there may be a considerable term due to solvation changes. The observed activation energy may thus be greater than that involved in the proton transfer alone, and the true height of the energy barrier may be somewhat less than that calculated. The ratio $E/E^* = 0{\cdot}79$ is thus a maximum value.

E/E^* is a measure of the degree of tunnelling. The more important the quantum mechanical leakage the smaller will be this ratio. The observed value is a little less than that obtained in the fluoride ion-catalysed bromination of ethyl 2-oxocyclopentanecarboxylate (0·81) and much smaller than those obtained with other catalysts in the latter reaction (0·88, 0·90),[3] or in the reactions between the trinitrobenzyl anion and acetic acid (0·93) [5] or hydrogen fluoride.[6] This is consistent with the much higher temperature at which the curvature has been observed in the present instance.

(*b*) *Width.* The calculations have assumed a symmetrical parabolic barrier of base $2a$. A nearer approximation to the width of a real barrier the curvature of which at the top is the same as the parabola would be about $3a$. Thus the calculated value of $a = 0{\cdot}563$ Å gives a barrier width of slightly less than 1·7 Å. This is a perfectly plausible distance for the proton to have moved in the course of the reaction, being of the same order as that between the two equilibrium positions of a hydrogen atom in an unsymmetrical hydrogen bond.[3]

The barrier width in this reaction is only slightly less than that calculated from the isotope effect in the bromination of ethyl 2-oxocyclopentanecarboxylate ($a = 0{\cdot}587$ Å).[1] As these reactions involve similar substrates under similar conditions this agreement indicates that the two methods of calculation are consistent. This is the first time this has been demonstrated. Previous calculations from the curvature of the Arrhenius plots gave values of a of between 0·73 and 0·83 Å.[5,6] There appeared to be a discrepancy between the two methods. However, these large values of a were obtained for reactions in ethanol.

[16] Bell, *Proc. Roy. Soc.*, 1935, *A*, **148**, 241.

[17] Caldin, *J.*, 1959, 3345.

Solvation of the reactants by the bulky ethanol molecules may prevent them from approaching as closely as they would in water. Calculations begun by Dr. M. Kasparian and extended by the author on the curvature of the Arrhenius plot for the fluoride ion-catalysed bromination of ethyl 2-oxocyclopentanecarboxylate in aqueous 5·2M-sodium bromide give a larger value of *a*, about 0·7 Å, than is found by the isotope method for this reaction in 0·2M-potassium bromide in deuterium oxide. This discrepancy may be explained as follows. In very concentrated salt solutions there is very little " free " solvent,[18] so that the solvating species is probably the hydrated sodium ion (more water will be associated with the small cation than with the large anion). The Na^+OH_2 complex will be larger than the simple water molecules and so prevent the reactants approaching so closely. This effect will be reinforced by the repulsion between the sodium ion and the incipient proton.

The small difference, about 0·02 Å, between the half-width obtained for this reaction and that for the anion-catalysed bromination of ethyl 2-oxocyclopentanecarboxylate may possibly be due to the rather smaller size of the water molecule compared with that of deuterium oxide used as solvent in the earlier work. The O–H and O–D bond lengths differ by about 0·05 Å.[19] However, because of the assumptions involved in these calculations, too much emphasis should not be laid on these comparatively small differences.

If the interpretation of these results is correct, a large isotope effect should be observed in this reaction. The ratio of the pre-exponential factors of the Arrhenius equation, A_D/A_H, should be large, certainly greater than 2, the maximum possible for classical proton transfer, and probably larger than 24, the value observed in the fluoride ion-catalysed bromination of ethyl 2-oxocyclopentanecarboxylate,[3] where the tunnelling may be rather less than in the present instance.

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[18] Hulett, *Trans. Faraday Soc.*, 1963, **59**, 1815.
[19] Sutton, *Chem. Soc. Special Publ.*, No. 11, 1958, M67.