Kinetic Isotope Effects in Proton-transfer Reactions

By J. R. JONES†

(*Chemistry Department, University of British Columbia, Vancouver* 8, *Canada*)

RECENT results for the base-catalysed exchange of some aromatic hydrocarbons in firstly[1] a medium of lithium cyclohexylamide in cyclohexylamine, and secondly,[2] dimethyl sulphoxide containing potassium butoxide as base, have indicated considerable discrepancies in the relative rates of proton exchange. Hofmann *et al.*[2] suggested that the difference was due to greater charge delocalisation in the more polar solvent, whilst Streitwieser[1] suggested that ionisation may not be the true rate-determining step in the alkoxide–Me_2SO system. Further evidence[3] in support of the latter viewpoint was apparently obtained when a k_D/k_T value of near unity resulted from the alkoxide-catalysed exchange of the methyl hydrogens of toluene, in sharp contrast to a k_H/k_D value in excess of 10 when the reaction was catalysed by lithium cyclohexylamide in cyclohexylamine.[4] The absence of an isotope effect during racemisation studies using the t-butoxide–Me_2SO system has also been observed.[5] The object of the present Communication is to show that the two widely different isotope effect values are not inconsistent and that both may relate to the same rate-determining ionisation mechanism. Also implicit in this statement is the fact that the use of Me_2SO–base media may be a means of determining transition-state structure.

For the ionisation of weak carbon acids in the presence of a base catalyst (B) it is convenient to use a linear three-centre model:—

$$AH + B^- \rightarrow [A \cdots\cdot H \cdots\cdot B]^{\ddagger} \rightarrow A^- + HB$$

Kinetic isotope effect theory[6] points to the fact that when the force constant (F_{22}) of the bond AH is equal to the force constant (F_{11}) of the bond HB the isotope effect will be a maximum. This condition is likely to be so when $pK_A(HA) - pK_A(BH)$ is zero,[7] and recently data has become available which seems to support this conclusion.[7,8] Although no accurate value of the pK_A of toluene is available it seems as if a value of 40 would be approximately correct. Similarly whilst no data is available for cyclohexylamine a similar solvent would be ammonia where a pK_A at 25° of 35 has been suggested[9] as compared to an experimentally obtained[10]

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† On leave of absence from University of Surrey, U.K.

value of 36. On this basis a large isotope effect of 10, which included a small secondary contribution, is not unexpected.

In the case of the t-butoxide–Me_2SO system the high basicity of the medium is due to the ability of Me_2SO to decrease the solvation of the butoxide ion. In other words for measurements in the t-butoxide–t-butyl alcohol–Me_2SO system the increase in the rate of ionisation as the concentration of Me_2SO is increased is due to the increasing ease with which the desolvation of the butoxide ion occurs. Consequently although the basicity of the medium as represented by H_- is increasing, the position of the proton in the transition state remains substantially the same. This viewpoint is reflected in the results of a study[11] of the reaction of 2-arylethyl bromide with $KOBu^t$ in Bu^tOH–Me_2SO, where k_H/k_D was found to remain constant within experimental error as the Me_2SO concentration increases, and also by unpublished results[12] of our own on the detritiation of acetophenone in OH^-–Me_2SO where a log k against H_- plot has a slope of $+0{\cdot}5$ and is consistent with the known transition-state structure.[13]

Although no accurate pK_A values in Me_2SO are available, it can be assumed that any changes in going from aqueous media to Me_2SO would be similar for both $PhCH_2^-$ and BuO^-. If a value of 20 for pK_A of Bu^tOH is taken[14] then $pK_A(HA) - pK_A(HB) \sim 20$, and as the anion of toluene will be a far more powerful base than the butoxide ion, the proton in the transition state will be very near the latter, the situation being $[A^- \cdot \cdot \cdot \cdot H^+B^-]$. Consequently a low value of k_H/k_D is to be expected, and if the condition $f\ddagger > \frac{\nu\ddagger_{HL}}{\nu\ddagger_{DL}} f_{HA} \cdot f_B$ prevails, where $\nu\ddagger_{HL}$ and $\nu\ddagger_{DL}$ are the decomposition modes of the vibrational frequencies (in wave-numbers), then an inverse isotope effect will obtained.[6]

Approximate calculations[15] of the magnitude of k_H/k_D can be made by taking $M_B = 17$, $M_H = 1$, and $M_A = 100$, and by assuming reasonable values of F_{11}/F_{22}, and a curvature parameter d, given by $F_{11}F_{22} - F_{12}^2$ of $-0{\cdot}1$. Although no direct measurement of the F_{11}/F_{22} ratio can be made, in view of the transition state suggested it would be expected that $F_{11} \gg F_{22}$, and the greater the difference $pK_A(SH) - pK_A(HB)$ then the greater the ratio F_{11}/F_{22} would become. For values of F_{11}/F_{22} in excess of 10, the values of k_H/k_D seem to show little change and for the case of $F_{11}/F_{22} = 10$ the resulting k_H/k_D value is $2{\cdot}0$, leading to k_D/k_T of near unity. Such a low value is therefore not incompatible with a rate-determining ionisation process.

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