Proton Transfer between 2,6-Di-t-butylpyridine and its Conjugate Acid in an Aprotic Solvent

Victor Gold* and Rosemary A. Lee

Department of Chemistry, King's College London, Strand, London WC2R 2LS, U.K.

The kinetics of the title reaction have been studied by n.m.r. line shape analysis of the signals due to the t-butyl group protons in the two reaction partners, with the conclusion that in this sterically-hindered system proton transfer from the pyridinium ion to the halide ion within a contact ion pair is a rate-limiting process, without any evidence for proton tunnelling according to usual criteria.

The kinetics and mechanisms of the rapid proton transfers between amines and their respective conjugate acids (ammonium ions) have been the subject of a series of brilliant studies by Grunwald and Meiboom and their associates.[1] The reactions were generally followed in hydroxylic solvents by observation of the line-broadening of the n.m.r. signal due to protons of the ammonium ion, and the dependence of the rates upon the (minute) concentration of amine was deduced from the effect of the concentration of acid in the system.

The present study examines the analogous interconversion of 2,6-di-t-butylpyridine (DBP), B, and its conjugate acid in CH_2Cl_2 solution. The substrate is a sterically hindered amine and, if the suspected connection between steric hindrance and proton tunnelling is valid, might be expected to exhibit, for

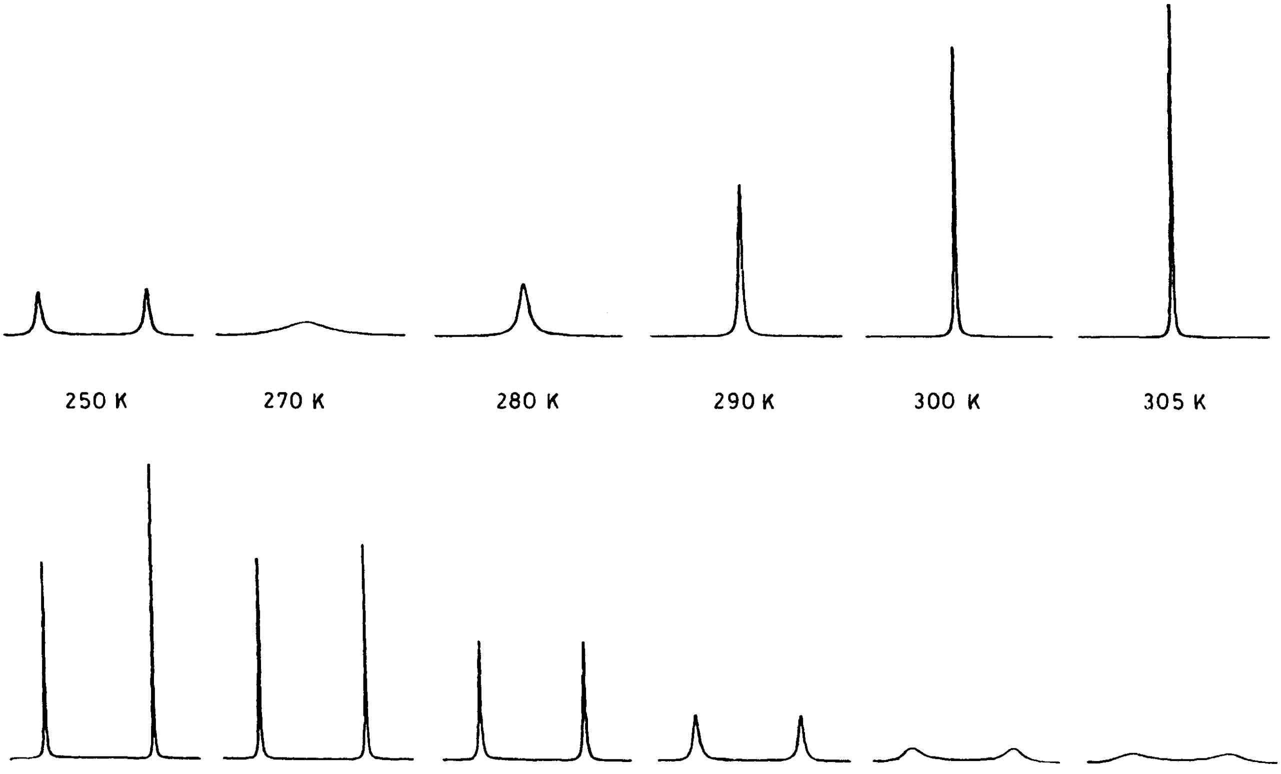

Figure 1. ^1H N.m.r. signals of t-butyl groups at different temperatures (upper set, B–BH·Cl; lower set, B–BH·Br).

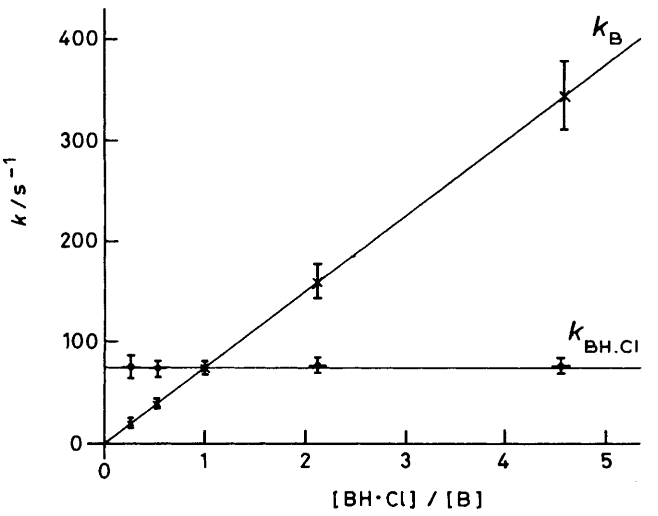

Figure 2. Dependence of k_B and $k_\mathrm{BH\cdot Cl}$ on concentration ratio [BH·Cl]/[B] at 260 K.

instance, an uncommonly large primary kinetic hydrogen isotope effect.[2] It has also been inferred that the use of an aprotic solvent of low permittivity would favour tunnelling.[3] The concomitant absence of hydroxylic species in our system also precludes the occurrence of termolecular proton transfers involving the participation of a solvent molecule as a 'bridge' for indirect proton transfer.[1]

The exchange between DBP and its conjugate acid was found to be sufficiently slow for the complete proton n.m.r. spectra of both species to be observable when the latter are present at approximately equal concentrations (*ca.* 0.05—0.2 M). Kinetic measurements were based on the line shapes of the signals associated with the t-butyl groups, studied as a function of temperature (Figure 1). The exchange is also noticeable for the NH proton signal but the line shape of this is additionally affected by quadrupole relaxation. Some less accurate observations were also made on systems containing protonated DBP and an excess of hydrogen halide; these results are consistent with the conclusions reported below.

We find that the observed first-order rate coefficient for chemical flux (ϕ)[4] out of the conjugate acid (equal to the reciprocal of the mean life time, τ, of that species) is independent of the concentration of the amine, and that the corresponding rate coefficient relating to the amine is proportional to the ratio of the concentration of the conjugate acid to that of the amine (Figure 2). Bearing in mind that in $\mathrm{CH_2Cl_2}$ solution the conjugate acid is expected to be predominantly in the form of the contact ion pair $\mathrm{BH^+X^-}$ (or BH·X), we write these kinetic results as shown in equations (1) and (2). We

$$\begin{aligned}\phi_{-\mathrm{B}} &= k_\mathrm{B}[\mathrm{B}] = \tau_\mathrm{B}^{-1}[\mathrm{B}]\\ &= k_1([\mathrm{BH\cdot X}]/[\mathrm{B}])[\mathrm{B}] \qquad (1)\end{aligned}$$

$$\begin{aligned}\phi_{-\mathrm{BH\cdot X}} &= k_\mathrm{BHX}[\mathrm{BH\cdot X}] = \tau_\mathrm{BHX}^{-1}[\mathrm{BH\cdot X}]\\ &= k_2[\mathrm{BH\cdot X}] \qquad (2)\end{aligned}$$

infer that the rate-limiting step for chemical flux out of BH·X is unimolecular and, since the ratio [BH·X]/[B] is proportional to the (low) concentration of free HX in the system, that the rate-limiting step for chemical flux out of B is a bimolecular reaction between amine and HX. (The solid salt formed from DBP and hydrogen chloride has the composition BH·ClHCl,[5] but significant concentrations of $\mathrm{HCl_2^-}$ do not co-exist with free base in solution.) The mechanism of the reaction is accordingly written as shown in equations (3) and (4) (where $k_\mathrm{d} = k_2$, $k_\mathrm{a} = k_1/K_\mathrm{dissoc.}$, and $K_\mathrm{dissoc.} = [\mathrm{HX}]\,[\mathrm{B}]/[\mathrm{BH\cdot X}]$).

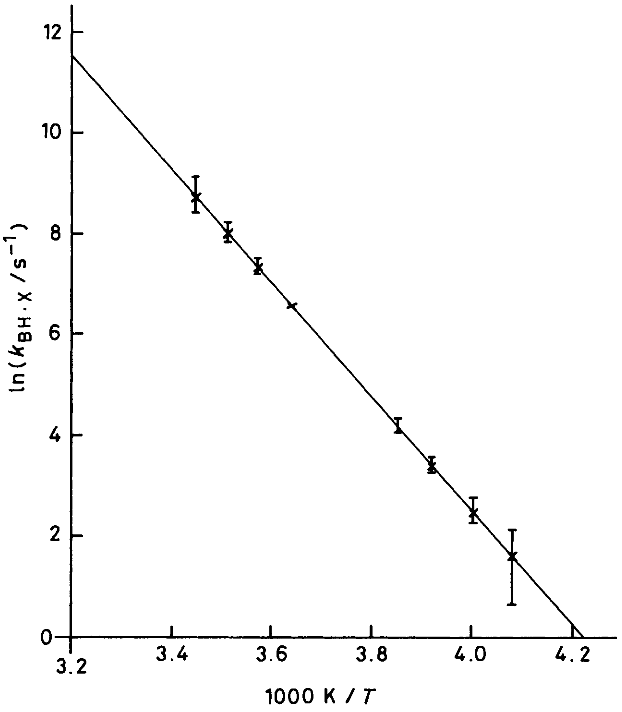

Figure 3. Arrhenius plot for $k_\mathrm{BH\cdot Cl}$ ([B] = [BH·Cl] = 1.3×10^{-3} M).

$$\mathrm{B}\mathit{H}\cdot\mathrm{X} \xrightarrow{k_\mathrm{d}} \mathrm{B} + \mathit{H}\mathrm{X} \qquad (3)$$

$$\mathrm{B} + \mathrm{HX} \xrightarrow{k_\mathrm{a}} \mathrm{BH\cdot X} \qquad (4)$$

The unimolecular reaction (3) of BH·X is visualised as a proton transfer within the contact ion pair. Its rate constant k_d is small, presumably because of the steric encumbrance of the $\geqslant$NH group. Whilst the kinetic laws would equally admit step (3) to be composite, involving ion-pair dissociation (3a) as the first phase, the implication of this scheme, that proton transfer (3b) between free $\mathrm{BH^+}$ and $\mathrm{X^-}$ should be preferred to direct proton transfer (3) within the contact ion-pair, does not seem tenable.

$$\mathrm{B}\mathit{H}\cdot\mathrm{X} \longrightarrow \mathrm{B}\mathit{H}^+ + \mathrm{X}^- \qquad (3a)$$

$$\mathrm{B}\mathit{H}^+ + \mathrm{X}^- \longrightarrow \mathrm{B} + \mathit{H}\mathrm{X} \qquad (3b)$$

The mechanism (3)—(4) bears some analogy to that proposed for less hindered amines in hydroxylic solvents,[1,6] given in equations (5)—(6). However, the two mechanisms

$$\mathrm{B}\mathit{H}\cdot\mathrm{OHR} + \text{solvent} \rightarrow \mathrm{B}\cdot\mathit{H}\mathrm{OR} + \mathrm{H^+_{solv.}} \qquad (5)$$

$$\mathrm{HOR} + \mathrm{B}\cdot\mathit{H}\mathrm{OR} \rightarrow \mathrm{B\cdot HOR} + \mathit{H}\mathrm{OR} \qquad (6)$$

are different because equations (5) and (6) assume that hydrogen-bonding to the nitrogen atom of the base B is maintained at all times and that reaction (6) is a displacement of hydrogen-bonded solvent molecules, whereas in reaction (3) the base B is set free. A reaction sequence (7)—(9) [in

$$\mathrm{B}\mathit{H}\cdot\mathrm{X} \rightarrow \mathrm{B}\cdot\mathit{H}\mathrm{X} \qquad (7)$$

$$\mathrm{HX} + \mathrm{B}\cdot\mathit{H}\mathrm{X} \rightarrow \mathit{H}\mathrm{X} + \mathrm{B\cdot HX} \qquad (8)$$

$$\mathrm{B\cdot HX} \rightarrow \mathrm{BH\cdot X} \qquad (9)$$

place of (3)—(4)] in which there is bimolecular displacement of hydrogen-bonded HX by free HX is not plausible in our

Table 1. Isotope effect on $k_{BH\cdot X}$ for BH·Cl at 270 K.

x_D[a]	$k_{BH\cdot X(obs.)}/s^{-1}$	$k_{BH\cdot X}/s^{-1}$[b]	$k_{BD\cdot X}/s^{-1}$[c]	$k_{BH\cdot X}/k_{BD\cdot X}$
0.881	134 ± 10	373 ± 10	102 ± 13	3.7 ± 0.6
0.900	138 ± 10	394 ± 10	110 ± 12	3.6 ± 0.5

[a] x_D = [BD·Cl]/([BD.Cl] + [BH·Cl]). [b] Rate constant in deuterium-free system at same concentration of amine salt as for $k_{BH\cdot X(obs.)}$. [c] Calc. from $k_{BH\cdot X(obs.)} = k_{BD\cdot X}\, x_D + k_{BH\cdot X}\, (1 - x_D)$.

system, since the total concentrations of amine and its conjugate acid are comparable and that of HX is very much lower. Whilst the bimolecular process (6) is credible for hydroxylic solvents, we would also note that the dissociation–association sequence (10)—(11), analogous to (3)—(4), does not appear to be ruled out for these solvents by the existing evidence.

$$B\cdot \mathit{H}OR \rightarrow B + \mathit{H}OR \qquad (10)$$

$$HOR + B \rightarrow B\cdot HOR \qquad (11)$$

The significant conclusion to be drawn from the quantitative experimental results is that the intra-ion-pair proton transfer (3) does not have the features of a tunnelling reaction, for the following reasons: (i) the reaction obeys the Arrhenius equation over a wide temperature range (Figure 3) and with a high energy of activation (E_a *ca.* 90 kJ mol^{-1} over the most accurate range, from 240 to 290 K for the chloride); (ii) use of *N*-deuteronated base in place of *N*-protonated base results in a *ca.* four-fold reduction in rate (primary kinetic isotope effect), as detailed in Table 1; (iii) the use of X = Br in place of X = Cl causes a *ca.* 400-fold reduction in rate, consistent with the fact that Br$^-$ is a weaker base than Cl$^-$ (for example, the rate constant $k_{BH\cdot X}$ for the hydrobromide of DBP at 290 K has the value 14.5 s^{-1}, whereas the corresponding value for the hydrochloride is 6000 s^{-1}).

Although our measurements relate to a nitrogen base of unusual steric hindrance and hence relatively low basicity,[5,7] we believe that the mechanism deduced may be of more general validity for proton transfers from ammonium ions derived from weakly basic amines in media of low permittivity.

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