Kinetics and Isotope Effects in Proton Transfers from 3-Bromo- and 3-Nitro-(+)-camphor

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The rates of mutarotation of 3-bromo-(+)-camphor and 3-bromo-3-deuterio-(+)-camphor have been measured in solutions of sodium hydroxide in 15—70% v/v dimethyl sulphoxide–water, and in 20 and 45% w/w dioxan–water. The rate increases sharply with dimethyl sulphoxide content, and the primary hydrogen isotope effect shows indications of a maximum at about 40% dimethyl sulphoxide. The same reaction was studied in glycine buffer solutions in 15% dimethyl sulphoxide and in the two dioxan–water mixtures. There is clear evidence for general base catalysis by the glycine anion, compared with which the effect of hydroxide ions is abnormally small.

The rates of bromination of 3-nitro-(+)-camphor and of 3-deuterio-3-nitro-(+)-camphor were measured in a variety of aqueous buffer solutions. The reaction is of zero order with respect to bromine and is catalysed by the basic buffer components. The p*K* of 3-nitro-(+)-camphor was found to be 3.54, and the isotope effect exhibits a marked maximum when the p*K* of the buffer acid is close to this value. The reactions of both isotopic species conform fairly well to Brönsted relations, but it is pointed out that the existence of a maximum in k^H/k^D must imply a deviation from a linear relation for at least one of the isotopic species, and the experimental results lend some support to this view.

DERIVATIVES of (+)-camphor substituted in the 3-position offer attractive possibilities for investigating rates of ionisation or enolisation, since the commonly used methods of scavenging with halogens or measuring rates of isotope exchange can be supplemented by studying rates of mutarotation. However, since the pioneer work of Lowry and his collaborators [1] there have been few kinetic investigations apart from the work of Bell and Sherred [2] on the acid-catalysed mutarotation of 3-nitro-(+)-camphor in chlorobenzene. The present paper reports a kinetic study of the base-catalysed mutarotation of 3-bromo-(+)-camphor in some mixed solvents and of the bromination of 3-nitro-(+)-camphor in aqueous solution, including the measurement of hydrogen isotope effects.

EXPERIMENTAL

Materials.—3-Bromo-(+)-camphor was prepared by addition of bromine to (+)-D-camphor, as described by Ingersoll and Babcock.[3] Recrystallisation from 95% ethanol gave a white solid, m.p. 75 °C (lit.,[4] 76 °C). The doublet at τ 5.5 in ^{1}H n.m.r. spectrum shows this to be the *endo*-isomer. For the mutarotation experiments it was partly converted into the *exo*-isomer by the method of Lowry *et al.*[5] in which the substance is equilibrated in ethanolic sodium ethoxide, acidified, and fractionally crystallised; the more soluble *exo*-isomer remains in the mother liquors. Repetition of this process eventually gave a product which, after sublimation at 0—5 °C and 1 mmHg, had α_{546}^{20} 43° and α_{365}^{20} 367° (4 g dm^{-3} in ethanol). Comparison of these figures with the known rotations of the pure isomers [4] showed that the product contained 60% of the *exo*-isomer, and this was confirmed by ^{1}H n.m.r. spectroscopy and g.l.c. (15% Carbowax on Chromosorb W at 140 °C).

For the preparation of 3-bromo-3-deuterio-(+)-camphor the *endo*-compound (10 g) was dissolved in dry dioxan (200 cm^3) and deuterium oxide (99.8% D_2O; 100 cm^3). A small piece of clean sodium was added and the solution was kept at 80 °C for 1 h. It was then acidified with hydrochloric acid and evaporated to dryness, and the residue was extracted with ether. This procedure gives an equilibrium mixture of *exo*- and *endo*-isomers, which were separated by preparative g.l.c. (Varian Autoprep 700; 10% Carbowax on Chromosorb W at 175 °C). The ^{1}H n.m.r. spectrum of the final product showed that the hydrogen atom in the group –CHBr– had been completely replaced by deuterium.

3-Nitro-(+)-camphor was obtained by oxidation with permanganate [6] of 3-hydroxyiminocamphor prepared by Claisen's method.[7] Recrystallisation from ethanol gave the pure product, m.p. 101 °C (lit.,[4] 103 °C), α_D^{20} $-109°$ (50 g dm^{-3} in benzene) (lit.,[6] $-104°$). This is the *endo*-isomer, and the equilibrium content of the *exo*-form is very low in solution, especially in aqueous media.

3-Deuterio-3-nitro-(+)-camphor was prepared by adding the above substance (5 g) to deuterium oxide (50 cm^3), followed by enough sodium deuteroxide to dissolve the compound. The nitrocamphor was then precipitated by acidifying with hydrochloric acid. After a repetition of this process the ^{1}H n.m.r. spectrum of the product showed that the group $-CHNO_2-$ had been completely deuteriated.

Deionised water was distilled from alkaline potassium permanganate, after which it was boiled for 30 min and cooled under nitrogen. Dimethyl sulphoxide was purified by treatment with molecular sieves and barium oxide, then distilled under reduced pressure, as described by Johnson.[8] Dioxan was dried with molecular sieves, refluxed with lithium aluminium hydride, and distilled.

Dichloroacetic acid was distilled at 100 °C and 20 mmHg and the concentrations of its solutions were determined by titration. DL-Mandelic acid was recrystallised from water (m.p. 118 °C; lit.,[4] 118 °C), and malonic acid sublimed at 100 °C and 10 mmHg (m.p. 137 °C; lit.,[4] 135.6 °C). The remaining buffer components were of AnalaR grade.

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[1] T. M. Lowry *et al.*, numerous papers in *J. Chem. Soc.*, 1898—1923.

[2] R. P. Bell and J. A. Sherred, *J. Chem. Soc.*, 1940, 1202.

[3] A. Ingersoll and S. H. Babcock, *J. Amer. Chem. Soc.*, 1938, **55**, 341.

[4] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965.

[5] T. M. Lowry, V. Steele, and H. Burgess, *J. Chem. Soc.*, 1922, 633.

[6] T. M. Lowry, *J. Chem. Soc.*, 1898, 986.

[7] L. Claisen and W. Manasse, *Annalen*, 1893, **273**, 71.

[8] M. D. Johnson, *J. Chem. Soc.*, 1965, 805.

Buffer solutions were prepared by adding standard sodium hydroxide solution to the acidic component of the buffer. Their pH values were checked (glass electrode), and the constancy of pH within a series was maintained if necessary by adding small quantities of hydrochloric acid. The ionic strength of the aqueous buffer solutions was made up to 0.2 mol dm^{-3} by adding potassium chloride. For the strongest acids (dichloroacetic, monochloroacetic, and mandelic) the stoicheiometric concentration of the anion was corrected by adding to it the appropriate hydrogen ion concentration, calculated from the measured pH and an assumed activity coefficient $f_{\pm} = 0.73$.

Determination of p*K for* 3-*Nitro*-(+)-*camphor at* 25 °C.—The absorbance at 317 nm (due to the anion) of 1×10^{-4}M-solutions in six phthalate buffers [9] was measured in the range pH 3.0 to 4.0. The absorbance in sodium hydroxide solution was also measured, in order to obtain the molar absorptivity of the anion. The mean of the six experiments gave pK_{SH} 3.54 ± 0.01, assuming $f_{\pm} = 0.758$ at $I = 0.1$ mol dm^{-3}.

Rate of Mutarotation of 3-*Bromo*-(+)-*camphor*.—This was studied with a Perkin-Elmer 141 polarimeter, which could be read to ±0.001°, or linked to an automatic data acquisition system. Measurements were made at 365 nm, and the change in rotation was typically from 1.8 to 2.0°. The mutarotation followed a strictly first-order course, and velocity constants were calculated either from a plot of $\ln(r_\infty - r)$ against t, or by employing a version of the general least squares program LETAGROP VRID of Sillén,[10] in which the initial and final rotations and the velocity constant are all treated as parameters to be determined.

Rate of Bromination of 3-*Nitro*-(+)-*camphor*.—This was determined by following the decrease in absorbance by the tribromide ion at 330 nm with a Gilford 2400 recording spectrophotometer. Typical concentrations were [nitrocamphor] 10^{-4} mol dm^{-3}, $[\text{Br}_3^-] + [\text{Br}_2]$ 2×10^{-4} mol dm^{-3}, $[\text{Br}^-]$ 0.1 mol dm^{-3}. The total fall in bromine concentration corresponded accurately to the formation of a monobromo-derivative. The reactions followed a strictly first-order law, showing that the rate is independent of bromine concentration, and the velocity constants were obtained from plots of $\ln(A_t - A_\infty)$ against t, where A is the absorbance. In one set of measurements in acetate buffers at pH 5.75 the rate of ionisation was followed directly (without the addition of bromine) by observing the increase in absorbance at 313 nm due to the anion.

Bromination of 3-*Bromo*-(+)-*camphor*.—This was found to be first order with respect to bromine, at least up to 6×10^{-3} mol dm^{-3} bromine, and a scavenging technique therefore could not be used for measuring the rate of ionisation of this compound.

RESULTS AND DISCUSSION

Kinetic Analysis.—For the mutarotation of the undeuteriated 3-bromo-(+)-camphor the kinetic scheme is as in (i), where the values of the first-order constants depend on the concentrations of acids and bases present

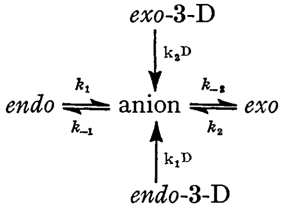
$$\textit{endo} \underset{k_1}{\overset{k_1}{\rightleftharpoons}} \text{anion} \underset{k_2}{\overset{k_2}{\rightleftharpoons}} \textit{exo} \qquad \text{(i)}$$

in the system and the concentration of the anion is throughout vanishingly small. It is easily shown that for the approach to equilibrium from any initial concentrations of the *endo*- and *exo*-isomers the change of rotation will follow a first-order law with a velocity constant k given by equation (1). For the present system this expression can be simplified considerably.

$$k = (k_1k_{-2} + k_2k_{-1})/(k_{-1} + k_{-2}) \qquad (1)$$

For camphor itself the observed rate of uptake of deuterium in the *endo*- and *exo*-positions [11] shows that $k_{-1}/k_{-2} = 21$, and a larger value is probable for 3-bromo-(+)-camphor, since its ^{1}H n.m.r. spectrum [12] indicates interaction between the bromine atom and the methyl group: a value of 28 for k_{-1}/k_{-2} was found for 3-nitro-(+)-camphor in the present study (see below). Further, measurements of specific rotation [5,13] and ^{1}H n.m.r. data give a value of about 25 for the equilibrium ratio $K = [\textit{endo}]/[\textit{exo}]$, which is equal to $k_{-1}k_2/k_1k_{-2}$. With the assumptions $k_{-1}/k_{-2} \gg 1$ and $K \gg 1$, equation (1) reduces to $k = k_2$, which should be accurate to within a few per cent. The same result can be reached without invoking the value of K if we assume $k_{-1}/k_{-2} \gg 1$ and $k_1/k_2 \approx 1$. The values of k_1 and k_2 are indistinguishable for 3-nitro-(+)-camphor (see below), and the same is likely to be the case for the bromo-compound.

For the mutarotation of 3-bromo-(+)-camphor in an aqueous medium the reaction scheme is (ii). This will



(ii)

not in general lead to first-order kinetics, though in practice no deviations from a first-order law were detected. This indicates that the rate-determining step is the removal of a deuteron from the deuteriated compound, the anion then being ' scavenged ' by the solvent or other acidic species to give preponderantly the *endo*-isomer. Further, since these experiments were carried out with almost pure *exo*-3-D-isomer, the observed velocity constant will be very close to k_2^{D}, especially since it is likely that $k_1^{\text{D}} \approx k_2^{\text{D}}$, as explained in the preceding paragraph. The observed values of k for the deuteriated and undeuteriated compounds can

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[9] R. A. Robinson and R. H. Stokes, ' Electrolyte Solutions,' Butterworths, London, 1959, p. 547.

[10] L. G. Sillén, *Acta Chem. Scand.*, 1962, **16**, 159; 1964, **18**, 1085.

[11] T. T. Tidwell, *J. Amer. Chem. Soc.*, 1970, **92**, 1448; S. P. Jindal, S. S. Sohoni, and T. T. Tidwell, *Tetrahedron Letters*, 1971, 779.

[12] W. D. Kumler, J. N. Shoolery, and F. V. Brutcher, jun., *J. Amer. Chem. Soc.*, 1958, **80**, 2533.

[13] T. M. Lowry and V. Steele, *J. Chem. Soc.*, 1915, 1382.

therefore be combined directly to give the isotope effect for proton or deuteron transfer from the *exo*-isomer.

The position is simpler for the bromination of 3-nitro-(+)-camphor. Since the reaction was found to be of zero order with respect to bromine, the observed rate must refer to the removal of a proton or deuteron from the substrate (k_1 or k_2 in the above analysis). It was originally supposed [6] that one of the forms of 3-nitro-(+)-camphor was the *aci*-nitro-isomer, but it is now clear [2] that only the *endo*- and *exo*-isomers can be isolated. The material used in the bromination experiments was essentially the *endo*-isomer, so that the velocity constant is k_1. Acidification of a solution of the sodium salt gave a product with [*exo*]/[*endo*] 28, which represents a minimum value for k_{-1}/k_{-2}. Kinetic experiments with mixtures of *exo*- and *endo*-isomers showed no deviations from first-order behaviour even at >90% conversion, showing that $k_1 = k_2$; the presence of a little *exo*-isomer in the main kinetic experiments will therefore not affect the results.

Results for 3-*Bromo*-(+)-*camphor*.—The rate of mutarotation was measured in seven mixtures of dimethyl sulphoxide (DMSO) and water containing between 15 and 70% v/v DMSO. For each solvent eight concentrations of sodium hydroxide were used, the ranges varying from 2×10^{-3}—4×10^{-2}M for 15% DMSO to 1×10^{-4}—4×10^{-3}M for 70% DMSO. Measurements were also made for the undeuteriated compound in 20 and 45% w/w dioxan–water ($[OH^-]$ 1×10^{-3}—8×10^{-3}M). For each system the results could be accurately represented by $k = k_{OH}[OH^-]$; *i.e.* there is no detectable water reaction. The values of k_{OH}^H and k_{OH}^D are collected in Table 1.

TABLE 1

Mutarotation of 3-bromo-(+)-camphor in alkaline solutions at 25 °C

% DMSO (v/v)	k_{OH}^H/ dm^3 mol^{-1} s^{-1}	k_{OH}^D/ dm^3 mol^{-1} s^{-1}	k_{OH}^H/k_{OH}^D
15	0.54	0.078	6.9
25	0.69	0.101	6.8
35	1.08	0.147	7.4
45	1.72	0.245	7.0
50	2.28	0.346	6.6
60	5.72	0.87	6.6
70	20.1	3.23	6.2
% Dioxan (w/w)			
20	0.42		
45	0.49		

The reaction rate shows a sharp increase with DMSO content, as is commonly observed for reactions involving hydroxide ions. By using published values of the acidity function H_- for these media [14,15] it is possible to construct a ' Brönsted plot ' of slope (β) 0.45 relating the effects of solvent composition on the reaction velocity and on the basic strength of the hydroxide ion, as was done previously by Bell and Cox [16] for the mutarotation of menthone. However, the value of such correlations is doubtful, since many cases are now known [17] in which changes of solvent composition have a large effect on reaction velocities but very little effect on equilibrium constants.

Owing to insufficient solubility this compound could not be studied in pure water, but a short extrapolation of the results in the mixed solvents gives $k_{OH}^H \approx 0.4$ dm^3 mol^{-1} s^{-1}, which may be compared with 0.06 for acetone,[18] 0.01 for menthone,[17] and 4.6 for monochloroacetone,[19] each corrected statistically for the number of equivalent protons. The observed isotope effect shows some indication of a maximum at about 40% DMSO, the variation resembling that found for the reaction of 3-nitro-(+)-camphor with a series of bases covering a similar range of basic strength (Table 3).

Measurements were also made in glycine buffers in 15% v/v DMSO and in 20 and 45% w/w dioxan. Three different buffer ratios were used, with three different buffer concentrations (in the range $[NH_2{\cdot}CH_2{\cdot}CO_2^-]$ 0.06—0.4 mol dm^{-3}) for each ratio. In each solvent the observed velocity constants agree well with equation (2)

$$k = k' + k_B[B] \qquad (2)$$

where B is the basic constituent of the buffer, and k' (but not k_B) depends upon the buffer ratio. The results are summarised by the values of k' and k_B given in Table 2. The expression k_{OH}/k_B has the values 2.6×10^3 and 4.8×10^3 for 20 and 45% dioxan, respectively.

TABLE 2

Mutarotation of 3-bromo-(+)-camphor in glycine buffers 25 °C

$r = [\overset{+}{N}H_3{\cdot}CH_2{\cdot}CO_2^-]/[NH_2{\cdot}CH_2{\cdot}CO_2^-]$, k_B in dm^3 mol^{-1} s^{-1}

	15% v/v DMSO $10^4 k_B = 2.1$	20% w/w dioxan $10^4 k_B = 1.6$	45% w/w dioxan $10^4 k_B = 1.00$
r	$10^5 k'$/s^{-1}	$10^5 k'$/s^{-1}	$10^5 k'$/s^{-1}
0.111	11.6	7.7	2.4
0.250	5.9	3.4	1.1
0.435	3.0	1.6	0.7

Accurate values of K_w and k_a (glycine) are available for these media.[20,21] If we define the dissociation constant of water (the conjugate acid of OH^-) in the mixed media as $K_a(H_2O) = K_w/[H_2O]$ we find $K_a(\text{glycine})/K_a(H_2O) = 1.4 \times 10^7$ and 1.0×10^7 for 20

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[14] K. Bowden, *Chem. Rev.*, 1966, **66**, 119.

[15] A. F. Cockerill and J. E. Lamper, *J. Chem. Soc.* (*B*), 1971, 503.

[16] R. P. Bell and B. G. Cox, *J. Chem. Soc.* (*B*), 1970, 194.

[17] B. G. Cox and A. Gibson, *Chem. Soc. Faraday Symposia*, 1975, **10**, p. 107.

[18] R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.

[19] R. P. Bell and H. C. Longuet-Higgins, *J. Chem. Soc.*, 1946, 636.

[20] H. S. Harned and L. D. Fallon, *J. Amer. Chem. Soc.*, 1939, **61**, 2374.

[21] H. S. Harned and C. M. Birdsall, *J. Amer. Chem. Soc.*, 1943, **65**, 1117.

and 45% dioxan, respectively, where activity coefficients cancel out to a first approximation. The effective Brönsted exponents (β) are hence 0.47 and 0.53 in these media. It is well established that proton abstractions by a series of carboxylate ions are characterised by $\beta \approx 0.8$,[18] so that the observed values of k_{OH} are lower by a factor of about $10^{3.5}$ than would be predicted by extrapolating such a series. Such behaviour is of course well known for proton abstraction from carbon acids: thus a compilation by Kresge [22] reveals discrepancies in the range $10^{2.7}$ to $10^{3.7}$ for five ketones.

The values of k' for aqueous dioxan are somewhat higher than those predicted from k_{OH} and $[\mathrm{OH}^-]$ calculated from the known equilibrium constants. This discrepancy cannot be attributed to proton abstraction by water, and is probably due to incomplete cancellation of activity coefficients.

Values of K_{w} and K_{a}(glycine) are not available for interpreting the rates in 15% DMSO, though some unpublished work [23] suggests that K_{w} differs little from the value in pure water. In aqueous solution [24] $K_{\mathrm{a}}(\text{glycine})/K_{\mathrm{a}}(\mathrm{H_2O})$ is 1.1×10^7, close to the corresponding values in both dioxan–water mixtures, and if the same value is assumed for 15% DMSO we arrive at $\beta = 0.48$ by combining this value with $k_{\mathrm{OH}}/k_{\mathrm{B}} = 2.6 \times 10^3$. The same conclusions follow about the low value of k_{OH}, and the observed values of k' in 15% DMSO are consistent with this assumption.

Results for 3-*Nitro*-(+)-*camphor*.—The rate of bromination was studied at a single buffer ratio close to unity and four buffer concentrations covering at least a five-fold range. In addition measurements with the undeuteriated compound were made in acetate buffers of pH 4.69, and as a check the rate of formation of the anion was observed directly at pH 5.63. Concordant results were obtained at all three buffer ratios. For a given buffer system the results could be represented accurately by equation (2), but k' was now found to be independent of pH and of the nature of the buffer. It can therefore be identified with k_0, the water-catalysed rate. The mean values for the two isotopic species are k_0^{H} 0.049 ± 0.006 $\mathrm{s^{-1}}$ and k_0^{D} 0.011 ± 0.001 $\mathrm{s^{-1}}$, the former being identical with the observed rate in 0.005—0.2M hydrochloric acid (0.050 ± 0.002 $\mathrm{s^{-1}}$; mean of 8 experiments).

The results are summarised in Table 3. $\Delta\mathrm{p}K'$ is defined by equation (3), in which 3.54 is the measured pK of 3-nitro-(+)-camphor, and the last term represents

$$\Delta\mathrm{p}K' = 3.54 - \mathrm{p}K(\mathrm{BH}) + \lg(q_{\mathrm{B}}/p_{\mathrm{BH}}) \qquad (3)$$

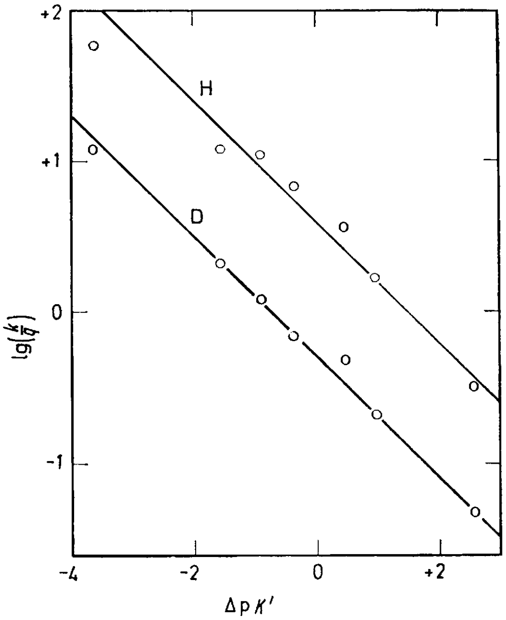
a statistical correction for the number of equivalent protons or proton-accepting sites in BH and B respectively. We have followed Gold and Waterman [25] in taking $q = 2$ for the hydroxide ion to allow for the presence of two equivalent but spatially different sites. The values of pK for the buffer components are taken from the compilation of Kortüm *et al.*,[26] and $K(\mathrm{H_2O})$ is given the conventional value of $K_{\mathrm{w}}/55.5$.

TABLE 3

Bromination of 3-nitro-(+)-camphor in aqueous solution at 25 °C

Base	$k_{\mathrm{B}}^{\mathrm{H}}$/dm^3 mol^{-1} s^{-1}	$k_{\mathrm{B}}^{\mathrm{D}}$/dm^3 mol^{-1} s^{-1}	$k_{\mathrm{B}}^{\mathrm{H}}/k_{\mathrm{B}}^{\mathrm{D}}$	$\Delta\mathrm{p}K'$
$\mathrm{H_2O}$	0.049/ 55.5	0.011/ 55.5	4.5	+5.10
$\mathrm{CHCl_2{\cdot}CO_2^-}$	0.63	0.098	6.4	+2.58
$\mathrm{CH_2Cl{\cdot}CO_2^-}$	3.29	0.415	7.3	+0.97
$\mathrm{PhCH(OH){\cdot}CO_2^-}$	7.2	0.96	7.5	+0.47
$\mathrm{PhCO_2^-}$	13.4	1.87	7.2	−0.36
$\mathrm{MeCO_2^-}$	23.6	3.43	6.8	−0.91
$\mathrm{CH_2(CO_2^-)_2}$	49.0	8.4	5.8	−1.55
$\mathrm{HPO_4^{2-}}$	176	52.0	3.4	−3.59

Table 3 shows that the magnitude of the isotope effect varies smoothly with $\Delta\mathrm{p}K'$, passing through a clear maximum in the neighbourhood of $\Delta\mathrm{p}K' = 0$. Similar behaviour has been observed for proton and deuteron abstraction from ethyl nitroacetate,[27] and model calculations [28] suggest that the variations in $k^{\mathrm{H}}/k^{\mathrm{D}}$ are attributable to variations in the tunnel correction



Brönsted relations for proton (deuteron) abstraction from 3-nitro-(+)-camphor and 3-deuterio-3-nitro-(+)-camphor

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[22] A. J. Kresge, *Chem. Soc. Rev.*, 1973, **2**, 475.

[23] E. C. Steiner, quoted by C. D. Ritchie in ' Solvent–Solvent Interactions,' eds. J. F. Coetzee and C. D. Ritchie, Dekker, New York, 1969.

[24] B. B. Owen, *J. Amer. Chem. Soc.*, 1934, **56**, 24.

[25] V. Gold and D. C. A. Waterman, *J. Chem. Soc.* (*B*) 1968, 839.

[26] G. Kortüm, W. Vogel, and K. Andrussov, ' Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London 1961.

[27] R. P. Bell and D. J. Barnes, *Proc. Roy. Soc.* 1970, *A*, **318**, 421.

[28] R. P. Bell, W. H. Sachs, and R. L. Tranter, *Trans. Faraday Soc.*, 1971, **67**, 1995.

rather than in the real frequencies of the transition state, as originally suggested by Westheimer.[29]

The values of either $k_B{}^H$ or $k_B{}^D$ are correlated with $\Delta pK'$ by the usual type of Brönsted relation [equation (4)], with β 0.40 for both isotopes, as shown in the

$$\lg(k_B/q) = \beta\Delta pK' + \text{constant} \qquad (4)$$

Figure. However, since $k_B{}^H/k_B{}^D$ passes through a maximum near $\Delta pK' = 0$ it is impossible in principle for the Brönsted plots for both species to be strictly linear in this region. In fact, the points for $k_B{}^H$ are better represented by a curve concave to the $\Delta pK'$ axis, while curvature is barely detectable for $k_B{}^D$. There are few investigations of isotope effects for proton transfer reactions in the neighbourhood of $\Delta pK' = 0$, and curvature can easily be obscured by individual deviations from the Brönsted relation, as in earlier work [27,30] on proton transfers from ethyl nitroacetate, which employed bases of widely different structural types.

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[29] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265.

[30] R. P. Bell and T. Spencer, *Proc. Roy. Soc.* 1959, *A*, **251**, 41.