Kinetic Hydrogen Isotope Effects for Proton Transfer between Carboxylic Acids and the Monoprotonated Cryptand (2,1,1)H$^+$ in Methanol

Brian G. Cox * and **Nguyen van Truong**
Chemistry Department, University of Stirling, Stirling FK9 4LA, Scotland
Hermann Schneider *
Max-Planck-Institut für biophys. Chemie, D-3400 Göttingen, West Germany

The rates of proton transfer from substituted acetic and benzoic acids, HA, to the monoprotonated cryptand (2,1,1)H$^+$ have been measured in methanol. The reaction involves a slow direct proton transfer from HA into the ligand cavity to give the di-*endo*-protonated cryptand (2,1,1)H$_2$$^{2+}$. The measured rates are several orders of magnitude lower than those expected for diffusion-controlled proton transfer between oxygen and nitrogen bases. Good Brönsted plots with α values close to 0.5 are observed for both series of acids. The reactions show substantial kinetic hydrogen isotope effects which pass through a maximum with increasing strength of HA.

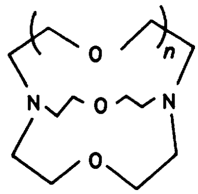
Proton transfer between electronegative atoms such as oxygen and nitrogen is usually very fast, and measurements of kinetic hydrogen isotope effects are rare.[1] A maximum in the dependence of the isotope effects upon acid strength of the donor has been observed for reactions in which proton transfer occurs after an unfavourable equilibrium, as part of a complex reaction scheme.[2,3] However, a detailed interpretation of the maxima is complicated by the fact that the proton transfer step is only free from a dominant influence of the accompanying diffusion steps when the pK_a values of the proton donor and acceptor differ by < *ca.* 2 pK units. Very small isotope effects (k^H/k^D *ca.* 1) have been found for ' slow ' transfers involving derivatives of 1,8-diaminonaphthalene in which the protons are involved in strong intramolecular hydrogen-bonding.[4]

Macrobicyclic cryptand ligands[5] provide particularly convenient examples of systems for which slow proton transfer reactions may be studied. Kinetic investigations[6-9] of the protonation reactions have shown that they occur in two distinct steps, corresponding to formation of mono- and di-protonated species. The rates for the (1,1,1) cryptand (I) are extremely slow and several different species have been observed by n.m.r. spectroscopy, interconverting over periods of hours.[9] It was suggested that the mono- and di-protonated species can exist in various conformers differing in whether the nitrogens are *endo* or *exo*.

We have recently investigated proton transfer with the (2,1,1) cryptand (II) in acid solution.[10] The monoprotonation of (II) is fast, but the second protonation step is sufficiently slow to be studied conveniently by stopped-flow methods in a number of solvents [equation (1)]. The reactions, although much faster than those of the (1,1,1) system, are still several orders of magnitude lower than those expected for a diffusion-controlled reaction in the thermodynamically favoured direction.[1] The crystal structure of the product (2,1,1)H$_2$$^{2+}$, trapped in the solid state as its diperchlorate salt, shows it to be the di-*endo*-protonated cryptand.[10]

$$\mathrm{LH^+ + HA \underset{k_A}{\overset{k_{HA}}{\rightleftharpoons}} LH_2{}^{2+} + A^-} \qquad (1)$$

In this paper we present results of a detailed study of the rates and kinetic hydrogen isotope effects for proton transfer between carboxylic acids and (2,1,1)H$^+$ in methanol. Some results for the proton transfer reactions in other solvents are also reported.



(I) $n = 1$ (1,1,1)

(II) $n = 2$ (2,1,1)

Experimental and Results

Materials.—Cryptands (2,1,1), (2,2,1), and (2,2,2) were purchased from Merck and used without further purification. Checks for purity have been described earlier.[7] The acids used (see Tables) were commercial samples of AnalaR or equivalent grade and used without further purification, except for 4-chlorobenzoic acid (Aldrich; $\geqslant$97%) which was recrystallized twice from distilled water and dried overnight at 95 °C. The purification of the solvents methanol, ethanol, dimethyl sulphoxide, acetonitrile, and propylene carbonate has been described elsewhere.[11,12]

Methan[^{2}H]ol (Aldrich; >99.5 atom % D) was used as purchased. Solutions of the acids in MeOD were prepared by dissolving the protio-acid, HA, in MeOD; the final composition of the solvent was always $\geqslant$99 atom % D (n.m.r.). In some cases MeOD was recovered and purified by distillation as for MeOH.

A sodium methoxide solution used in pK_a measurements was prepared by dissolving metallic sodium in methanol. The resulting solution was filtered and standardized by titration against HCl. Tetraethylammonium methoxide in methanol was prepared by adding aqueous tetraethylammonium hydroxide (Aldrich; 20%) to methanol. At the concentrations used in kinetic experiments the amount of water introduced in this manner was $\leqslant$0.08 w/v %. Tetraethylammonium acetate in methanol was prepared similarly by adding to methanol an appropriate volume of an aqueous solution of NEt_4OAc (from acetic acid with NEt_4OH). Water concentrations in the solutions used in kinetic experiments were $\leqslant$0.04 % w/v. A study of the effect of added water to methanol solutions on the kinetics of reactions involving benzoic acid was carried out and effects were shown to be negligible at water concentrations below 0.5 % w/v.

pK_a *Determinations.*—pK_a Values in methanol for a number of the acids used were not available. In order to ensure that the values were internally consistent and to check the method,

Table 1. pK_a Values [a] for acids in methanol at 25 °C

Acid	pK_a	Acid	pK_a
Acetic	9.56	4-Chlorobenzoic	8.88
3-Chloropropionic	9.00	3-Chlorobenzoic	8.72
2-Chloropropionic	7.87	3,4-Dichlorobenzoic	8.43
Chloroacetic	7.76	4-Nitrobenzoic	8.30
Cyanoacetic	7.41	3-Nitrobenzoic	8.20
Dichloroacetic	6.36	4-Chloro-3-nitrobenzoic	7.97
4-Hydroxybenzoic	9.75	3,5-Dinitrobenzoic	7.27
Benzoic	9.22	$(2,1,1)H_2^{2+}$ (pK_1)	7.52

[a] ±0.05; values refer to zero ionic strength.

pK_a values were determined for all the acids used. The determinations were carried out using standard techniques of pH measurements with glass electrodes in methanol [13] as in cell (A). A radiometer PM 64 pH-meter was used for all measurements.

$$\begin{array}{c|c||c|c} \text{glass} & \mathrm{HA \rightleftharpoons H^+ + A^-} & \text{KCl sat. aqueous} & \text{calomel} \quad \text{(A)} \\ \text{electrode} & \text{in MeOH} & \text{solution} & \end{array}$$

The true pH is related to the observed pH, $(\mathrm{pH})_{\mathrm{obs}}$ (based on calibration of the glass electrode–calomel system in aqueous buffers), by equation (2).[13] pH Values were determined for a number of [HA]/[A⁻] ratios obtained by titrating NaOMe–MeOH into HA solutions in methanol and used in conjunction with equation (3) to determine pK_a(HA). The activity coefficient of HA, γ_{HA}, was assumed to be unity, and

$$\mathrm{pH} = (\mathrm{pH})_{\mathrm{obs}} + 2.34 \qquad (2)$$

$$\mathrm{p}K_a(\mathrm{HA}) = \mathrm{pH} + \log \frac{[\mathrm{HA}]\gamma_{\mathrm{HA}}}{[\mathrm{A}^-]\gamma_\pm} \qquad (3)$$

$$\log \gamma_\pm = -\frac{Z^2AI^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} + \frac{Z^2AI}{3} \qquad (4)$$

$\gamma_\pm$ values were calculated from the Davies equation (4),[14] where $A = 1.96$ for methanol at 25 °C and I = ionic strength. At the low ionic strengths used ($\leqslant 5 \times 10^{-4}$M), activity coefficient corrections were small. The electrode was checked in a methanolic chloroacetic acid–chloroacetate buffer before and after each titration to ensure that any drift in the observed reading was $\leqslant 0.02$ pH units.

For cryptand (2,1,1) the first dissociation constant of the diprotonated form $(2,1,1)H_2^{2+}$ is defined by equations (5) and (6). It was determined in two separate ways, starting with $(2,1,1)H_2(ClO_4)_2$ and free (2,1,1) in methanol. The procedures used were as follows. (a) Pure and dried crystals of $[(2,1,1)H_2](ClO_4)_2$ as prepared for *X*-ray structural determination [10] were dissolved in methanol and titrated by NaOMe–MeOH as for the carboxylic acids. The pK_1 was then calculated from equation (7), using values obtained from three separate titrations with initial $[(2,1,1)H_2^{2+}]$ varying between 3×10^{-4} and 7×10^{-4}M. Activity coefficients were again calculated using equation (4). (b) In an alternative procedure, the pK_1 of the diprotonated cryptand was determined by titration of (2,1,1) solutions in methanol with methanolic CH_3SO_3H solution. Beyond the first endpoint $[(2,1,1) \longrightarrow (2,1,1)H^+]$ the pH is controlled by equilibrium (5) and from the known stoicheiometry in the titration it is possible to calculate pK_1 from equation (7). Values determined by the two methods agreed to within ±0.03 pK units.

$$(2,1,1)H_2^{2+} \overset{K_1}{\rightleftharpoons} H^+ + (2,1,1)H^+ \qquad (5)$$

$$K_1 = \frac{a_{\mathrm{H}^+}\, a(2,1,1)\mathrm{H}^+}{a(2,1,1)\mathrm{H}_2^{2+}} \qquad (6)$$

$$\mathrm{p}K_1 = \mathrm{pH} + \log \frac{[(2,1,1)\mathrm{H}_2^{2+}]\gamma_{2+}}{[(2,1,1)\mathrm{H}^+]\gamma_+} \qquad (7)$$

In all measurements, the solutions titrated were contained in a jacketted cell whose temperature was maintained at 25 (±0.1) °C by circulating water.

Measured pK_a values are given in Table 1. Values for the carboxylic acids are in excellent agreement with earlier published values [15,16] where comparison is possible. The value for $(2,1,1)H_2^{2+}$[pK_1 7.52(±0.05)] is significantly lower than that reported by Speiss *et al.* [pK_1 8.46(±0.05)] [17] but the latter value refers to an ionic strength of 0.05M. A strong dependence in the observed direction of the p$K_a(2,1,1)H_2^{2+}$ upon ionic strength is expected.

Kinetic Measurements.—There were in general no chromophores in either the acids or the cryptands useful for spectrophotometric detection. However, the reactions could be conveniently followed conductimetrically using a Durrum–Gibson stopped-flow apparatus. The conductance *versus* time data obtained during a kinetic run were digitized in a Datalab 901 Transient recorder in the form of 1024 eight-bit integers. There were transferred to a Commodore PET 3016 microcomputor, which performed a linear least-squares fit on the data to calculate the pseudo-first-order rate constant. All measurements were carried out at 25(±0.2) °C. The majority of kinetic measurements involved the protonation of $(2,1,1)H^+$ in MeOH (or MeOD) and the kinetic treatment used is described in some detail below.

(i) *Protonation of* $(2,1,1)H^+$ *in* CH_3OH.—Solutions of $(2,1,1)H^+A^-$ for a given acid, HA, were prepared from (2,1,1) and HA, and reacted with a large excess (10—1 000 fold) of HA [equation (8)]. It may be shown that a simple first-order approach to equilibrium will be observed under two limiting conditions, (a) when HA is in sufficiently large excess or is sufficiently strong that the reaction goes to completion in the forward direction, and (b) when the reaction is observed close to equilibrium (typical relaxation conditions).[18]

$$\mathrm{HA} + (2,1,1)\mathrm{H}^+ \underset{k_{\mathrm{A}}}{\overset{k_{\mathrm{HA}}}{\rightleftharpoons}} (2,1,1)\mathrm{H}_2^{2+} + \mathrm{A}^- \qquad (8)$$

When condition (a) obtains, the observed kinetics are given by equations (9) and (10) as illustrated by the results shown in

$$-\mathrm{d}[(2,1,1)\mathrm{H}^+]/\mathrm{d}t = k_{\mathrm{obs}}[(2,1,1)\mathrm{H}^+] \qquad (9)$$

$$k_{\mathrm{obs}} = k_{\mathrm{HA}}[\mathrm{HA}] \qquad (10)$$

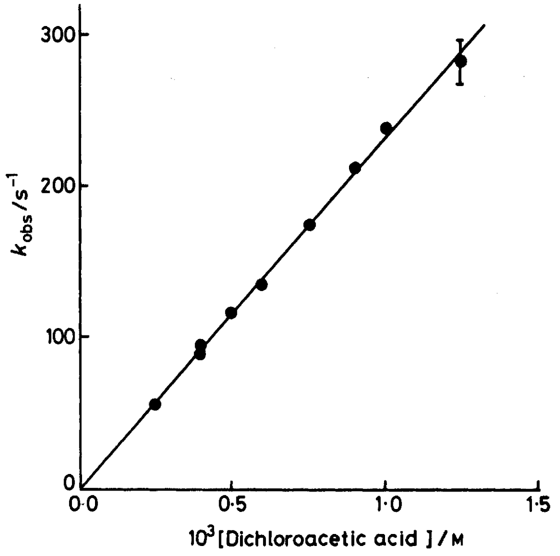


Figure 1. Rates of protonation of $(2,1,1)H^+$ by dichloroacetic acid in methanol at 25 °C

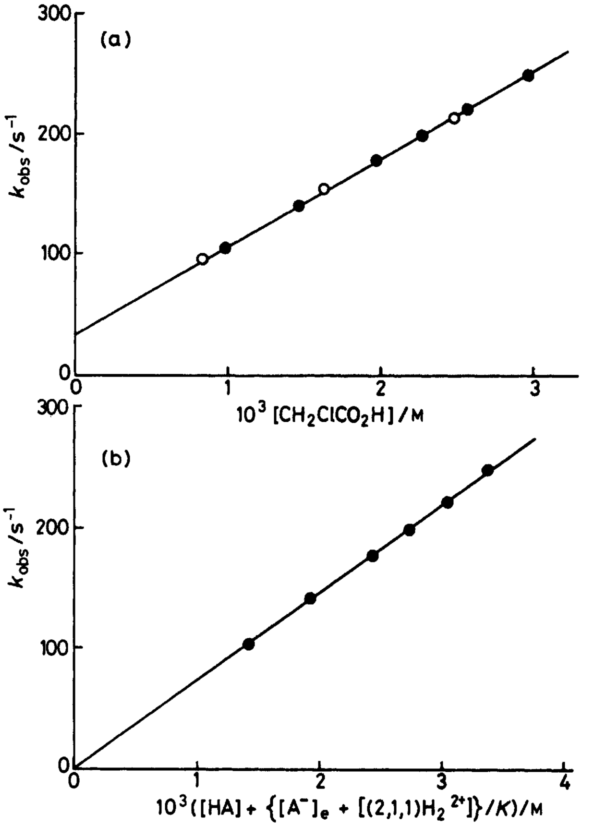


Figure 2. Protonation of $(2,1,1)H^+$ by chloroacetic acid in methanol at 25 °C. (a) ●, Reaction commencing with $(2,1,1)H^+$; ○, reaction commencing with (2,1,1). (b) Data plotted according to equation (12)

Figure 1 for the protonation of $(2,1,1)H^+$ by dichloroacetic acid. However, when the strengths of HA and $(2,1,1)H_2^{2+}$ are comparable or in particular when HA is weaker than $(2,1,1)H_2^{2+}$, the observed first-order rate constant is given by equation (11),[18] in which subscript e refers to equilibrium values.

$$k_{obs} = k_{HA}[HA] + k_A\{[(2,1,1)H_2^{2+}]_e + [A^-]_e\} \quad (11)$$

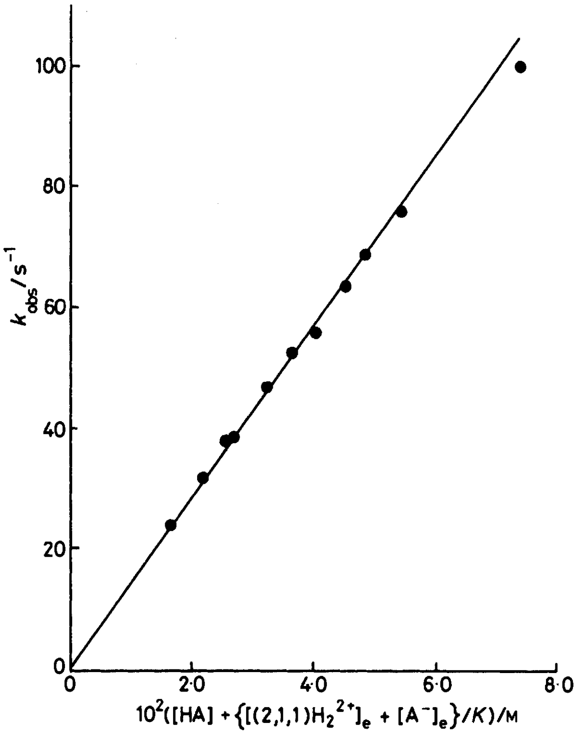


Figure 3. Rates of protonation of $(2,1,1)H^+$ by benzoic acid in methanol at 25 °C. Data plotted according to equation (12)

As a first approximation k_{HA} may be obtained from a plot of k_e {measured at constant total concentration of [(2,1,1)H]A} against [HA]. This plot has a slope of k_{HA} and intercept $k_A([(2,1,1)H_2^{2+}]_e + [A^-]_e)$. Figure 2(a) shows the results for chloroacetic acid {initial $[(2,1,1)HA] = 1.2 \times 10^{-4}$M} plotted in this way. Also included are three points determined using the free cryptand (2,1,1) as reactant. The results confirm that only the second protonation step is observed under these conditions.

In practice, however, values of $k_A\{[(2,1,1)H_2^{2+}]_e + [A^-]_e\}$ do not remain exactly constant in such a series, because equilibrium (8) is displaced increasingly to the right as [HA] increases. Thus a more exact analysis was preformed. Substituting in equation (11) for $k_A = k_{HA}/K$, where $K = K_{HA}/K_{(2,1,1)H_2^{2+}}$ is the equilibrium constant for (8), gives equation (12). Using the known equilibrium constant K (calculated from

$$k_{obs} = k_{HA}([HA] + \{[(2,1,1)H_2^{2+}]_e + [A^-]_e\}/K) \quad (12)$$

the data in Table 1) and the initial concentrations of HA and [(2,1,1)H]A it is possible to calculate $[(2,1,1)H_2^{2+}]_e$ and $[A^-]_e$. Then k_{HA} may be obtained from the slope of a plot of k_{obs} against $([HA] + \{[(2,1,1)H_2^{2+}]_e + [A^-]_e\}/K)$. Figure 2(b) shows the results for chloroacetic acid plotted in this manner. Rather wider variations in the concentrations of the various species were used to test the validity of equation (12) for weaker acids such as benzoic acid, where the reverse reaction makes a more significant contribution to the observed rates. Detailed results for protonation by benzoic acid are given in Table 2 and plotted according to equation (12) in Figure 3. Primary kinetic data are available for the other acids upon request.*

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* From B. G. C. or in Supplementary Publication No. SUP 23512 (6 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1983, Index 1.

Table 2. Protonation of $(2,1,1)H^+$ by benzoic acid in methanol at 25 °C

10^3 [HA]/ mol^{-1} dm^3	10^4 $[(2,1,1)HA]_i$ [a]/ mol^{-1} dm^3	10^4 $[A^-]_e$ [b]/ mol^{-1} dm^3	10^4 $[(2,1,1)H_2^{2+}]_e$ [b]/ mol^{-1} dm^3	k_e [c]/s^{-1}	k_e (calc) [d]/s^{-1}
11.0	1.45	2.17	0.73	38	36.7
16.4	1.45	2.30	0.85	47	46.5
23.7	1.45	2.41	0.96	56	58.1
30.7	1.45	2.48	1.03	69	69.1
36.5	1.45	2.52	1.08	76	77.6
54.8	1.45	2.62	1.17	100	105
13.0	0.26	0.48	0.22	24	24.0
13.0	0.77	1.28	0.51	32	32.0
13.0	1.28	2.00	0.72	38.5	38.0
13.0	2.04	2.99	0.95	47	46.6
13.0	2.53	3.61	1.06	52.5	52.5
13.0	3.83	5.11	1.28	64	64.4

[a] Initial concentration of [(2,1,1)H]A. [b] Equilibrium concentrations calculated using $K = 2.0 \times 10^{-2}$. [c] ±5%. [d] Rate constants calculated from equation (12) with $k_{HA} = 1.41 \times 10^3$ mol^{-1} dm^3 s^{-1} and $K = 2.0 \times 10^{-2}$.

Table 3. Kinetics of protonation of $(2,1,1)H^+$ by carboxylic acids in methanol at 25 °C

Acid (HA)	10^{-3} k_{HA} [a]/ mol^{-1} dm^3 s^{-1}	10^{-3} k_A [b]/ mol^{-1} dm^3 s^{-1}
Acetic	5.00	550
3-Chloropropionic	10.2	310
2-Chloropropionic	38.6	86
Chloroacetic	72.0	125
Cyanoacetic	84.3	65
Dichloroacetic	230	15.9
4-Hydroxybenzoic	0.563	96
Benzoic	1.41	70
4-Chlorobenzoic	1.63	37
3-Chlorobenzoic	2.17	34
3,4-Dichlorobenzoic	2.33	19
4-Nitrobenzoic	2.83	17
3-Nitrobenzoic	4.00	19
4-Chloro-3-nitrobenzoic	4.20	12
3,5-Dinitrobenzoic	10.8	6.1

[a] ±4%. [b] ±20%, obtained from $k_A = k_{HA}/K$. Values refer to zero ionic strength.

Table 4. Kinetics of protonation of $(2,1,1)D^+$ by carboxylic acids in CH_3OD at 25 °C

Acid (DA)	10^{-2} k^D_{DA} [a]/ mol^{-1} dm^3 s^{-1}	Acid (DA)	10^{-2} k^D_{DA} [a]/ mol^{-1} dm^3 s^{-1}
Acetic	15.0	4-Hydroxybenzoic	1.80
3-Chloropropionic	24.0	Benzoic	3.65
2-Chloropropionic	110	3-Chlorobenzoic	5.45
Chloroacetic	200	3,4-Dichlorobenzoic	5.76
Cyanoacetic	280	3-Nitrobenzoic	12.5
Dichloroacetic	1 050	3,5-Dinitrobenzoic	43.0

[a] ±4%.

Catalytic constants, k_{HA}, for various acids are summarized in Table 3. Also included are values of k_A, calculated from k_{HA} and K by $k_A = k_{HA}/K$. These values are necessarily less accurate than those of k_{HA} because of the errors in K (Table 1). The k_A value for acetate ion was measured directly by mixing an excess of tetraethylammonium acetate with $(2,1,1)H_2^{2+}$, the reactions again being followed conductimetrically using the stopped-flow apparatus. The observed value was $k_A = 3.5(\pm 0.3) \times 10^5$ mol^{-1} dm^3 s^{-1}, measured at an average ionic strength, I, of 5×10^{-4} mol dm^{-3}. Correction of this value to $I = 0$ gives $k_A = 5.2(\pm 0.5) \times 10^{-5}$ mol^{-1} dm^3 s^{-1}, in good agreement with the value obtained from $k_A = k_{HA}/K$ (Table 3).

One further check on the results involved the effect of added water on the measured rates. For the reaction between benzoic acid and $(2,1,1)H^+$ the addition of 0.5, 1, and 1.5% v/v of water resulted in a rate increase of 5, 11, and 18%, respectively, in the rate constant k_{HA}. Thus water concentrations below *ca.* 0.5% v/v have a negligible effect on the observed kinetics.

(ii) *Protonation of* $(2,1,1)D^+$ *in* CH_3OD.—The experimental techniques, ranges of concentration, and methods of analysis of the data are the same as those described above for measurements in MeOH. The only difficulty was in deciding upon the value of the equilibrium constant, K, to be used in equation (12), as pK_a values were not available in MeOD. Based on studies of weak acids in H_2O and D_2O [19,20] which show that for acids of similar strength ΔpK ($H_2O - D_2O$) is almost constant [*e.g.* for the carboxylic acids, ΔpK ($H_2O - D_2O$) = 0.47(±0.04)], we have assumed that the equilibrium constant K has the same value in MeOH and MeOD. The results are summarized in Table 4 and primary data are available on request. Values of k^D_{HA} catalytic constants for the forward reaction (8) in MeOD are insensitive to the exact value of K, as normally [DA] $\gg$ $(\{[(2,1,1)D_2^{2+}]_e + [A^-]_e\}/K)$ [equation (12)]. However, because k^D_A as determined from $k^D_A = k^D_{HA}/K$ are directly dependent upon the value chosen for K, we have not included them in Table 4. Within the limitations of the assumption concerning the equality of K in MeOH and MeOD, k^D_A values may be obtained from the results in Tables 1 and 4.

(iii) *Deprotonation of* $(2,1,1)H^+$ *by* CH_3O^- *in* CH_3OH.—The deprotonation of $(2,1,1)H^+$ by hydroxide ion in water is slow, consistent with the assumption that the proton is held within the cavity of the ligand.[7] Similar behaviour in methanol was confirmed by measurement of the rate of the corresponding reaction in methanol [equation (13)].

$$(2,1,1)H^+ + MeO^- \underset{k_o}{\overset{k_{OMe}}{\rightleftharpoons}} (2,1,1) + MeOH \qquad (13)$$

In the presence of excess of methoxide ion the observed kinetics were of simple first order as in equations (14) and (15).

Table 5. Rates of reaction between (2,1,1)H$^+$ and MeO$^-$ in methanol at 25 °C

10^4 [MeO$^-$]/ mol^{-1} dm^3	k_e/s^{-1}	k_e [a] (calc)/s^{-1}
2.15	0.305	0.292
4.30	0.351	0.353
7.20	0.430	0.437
8.60	0.482	0.477
10.7	0.533	0.537
14.3	0.638	0.640

[a] Calculated from equation (15) with $k_o = 0.23$ s^{-1} and $k_{OMe} = 2.87 \times 10^2$ mol^{-1} dm^3 s^{-1}.

Table 6. Kinetics of protonation of (2,1,1)H$^+$ by dichloroacetic acid (DCA) in various solvents at 25 °C

Solvent	Reaction conditions	10^{-3} k_{HA}/ mol^{-1} dm^3 s^{-1}
MeOH	[DCA] 2.5×10^{-4}—1.25×10^{-3}M [(2,1,1)H$^+$] 5×10^{-5}M	230
EtOH	[DCA] 2×10^{-4}—7.5×10^{-4}M [(2,1,1)H$^+$] 2×10^{-5}M	340
DMSO	[DCA] 1.5×10^{-3}—10^{-2}M [(2,1,1)H$^+$] 10^{-4}M	173
PC	[DCA] 10^{-3}—10^{-2}M [(2,1,1)H$^+$] 5×10^{-5}M	3.5
CH_3CN	[DCA] 2×10^{-3}—2.5×10^{-2}M [(2,1,1)H$^+$] 10^{-4}M	3.8

Concentrations of MeO$^-$ varied between 2×10^{-4} and 1.5×10^{-3}M, and the initial concentration of (2,1,1)H$^+$ [prepared from (2,1,1) and HCl] was *ca.* 4.5×10^{-5}M. The results are shown in Table 5, together with values of k_e calculated from equation (15) with $k_o = 0.23$ s^{-1} and $k_{OMe} = 2.87 \times 10^2$ mol^{-1} dm^3 s^{-1}. These values may be compared with the corresponding results in water,[7] which show values of $k_o = 1.59$ s^{-1}, and $k_{OH} = 1.08 \times 10^3$ mol^{-1} dm^3 s^{-1}.

$$-\mathrm{d}\{[(2,1,1)\mathrm{H}^+] - [(2,1,1)\mathrm{H}^+]_\infty\}/\mathrm{d}t = k_{obs}\{[(2,1,1)\mathrm{H}^+] - [(2,1,1)\mathrm{H}^+]_\infty\} \quad (14)$$

$$k_{obs} = k_o + k_{OMe}[\mathrm{OMe}] \quad (15)$$

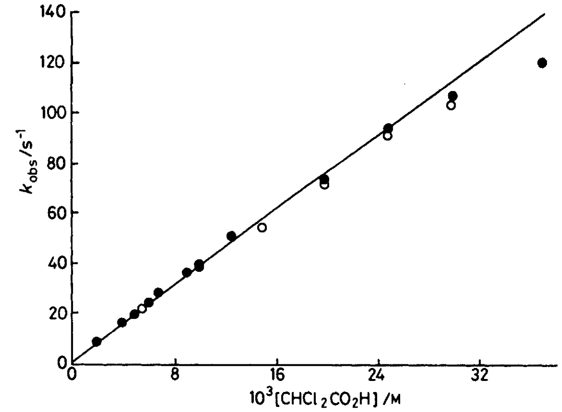

Figure 4. Rates of protonation of (2,1,1)H$^+$ by dichloroacetic acid in acetonitrile at 25 °C. ●, Reactions commencing with (2,1,1)H$^+$; ○, reactions commencing with (2,1,1)

Table 7. Kinetics of protonation of (2,1,1)H$^+$ by carboxylic acids in MeOH and MeOD at 25 °C

Acid	pK_a [a]	10^{-3} k^H_{HA}/ mol^{-1} dm^3 S^{-1} [b]	k^H_{HA}/k^D_{DA} [c]
Acetic	9.56	5.00	3.3_0
3-Chloropropionic	9.00	10.2	4.2_5
2-Chloropropionic	7.87	38.6	3.5_1
Chloroacetic	7.76	72.0	3.6_0
Cyanoacetic	7.41	84.3	3.0_1
Dichloroacetic	6.36	230	2.1_9
4-Hydroxybenzoic	9.75	0.563	3.1_2
Benzoic	9.22	1.39	3.8_6
4-Chlorobenzoic	8.88	1.63	
3-Chlorobenzoic	8.72	2.17	3.9_8
3,4-Dichlorobenzoic	8.43	2.33	4.0_5
4-Nitrobenzoic	8.30	2.83	
3-Nitrobenzoic	8.20	4.00	3.2_0
4-Chloro-3-nitrobenzoic	7.97	4.20	
3,5-Dinitrobenzoic	7.27	10.8	2.5_1

[a] pK_a (2,1,1)H_2^{2+} = 7.52 (±0.05). [b] ±4%. [c] ±8%.

(iv) *Solvent Effects on the Protonation of* (2,1,1)H$^+$ *by Dichloroacetic Acid.*—The rate of protonation of (2,1,1)H$^+$ by dichloroacetic acid (DCA) was also measured in ethanol, dimethyl sulphoxide (DMSO), propylene carbonate (PC), and acetonitrile. Dichloroacetic acid is sufficiently weak in all of these solvents to remain essentially undissociated at the concentrations used (see Table 6); in DMSO, pK_a = 5.6;[21] in PC, p$K_a \simeq 15$[12,22] and the value should be very similar in CH_3CN;[23] in EtOH the pK_a may be assumed to be at least as high as that in MeOH (6.36; Table 1). Thus the protonation reaction [equation (8)] is accompanied by a large increase in conductance. The reactions studied in the presence of excess of acid were always first order and plots of the observed first-order rate constant, k_e, against DCA were linear and passed through the origin. Figure 4 shows results obtained in CH_3CN, including values obtained when the free cryptand was mixed with DCA. The results are typical of those obtained in the various solvents and the zero intercepts suggest that under these conditions any reverse reaction may be neglected. The observed catalytic constants, k_{HA}, obtained from the slopes of plots such as shown in Figure 4 are listed in Table 7, together with a summary of the reaction conditions. Individual rate constants are available on request.

Discussion

Proton transfer reactions of cryptands are potentially very complex because of the possible involvement of various conformers, differing in whether the nitrogens are *endo* or *exo*. In the case of the (1,1,1) cryptand, studied by Lehn and Dye and their co-workers,[9] both internally and externally protonated nitrogen atoms play an important part in the overall kinetic behaviour.

The protolysis of (2,1,1), however, appears to be a much simpler process. The thermodynamically favoured state of the monoprotonated ligand is expected to be the *endo,endo* or (i,i) conformation by analogy with metal cryptates[5,24] and this is confirmed by its slow deprotonation by OH$^-$ in water[7] and by MeO$^-$ in methanol (Table 5). In both solvents the observed deprotonation rates are some seven orders of magnitude below that expected for a normal diffusion-controlled process.[1] An equilibrated (2,1,1)H$^+$ solution was used in almost all cases for kinetic studies on the second protonation

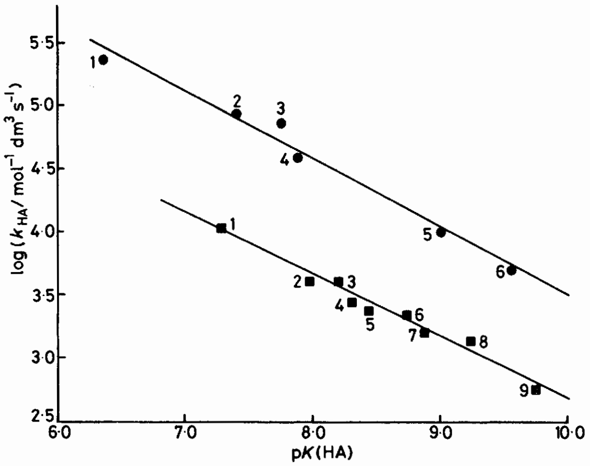

Figure 5. Brönsted plot for the protonation of $(2,1,1)H^+$ by acids HA. ●, Substituted acetic acids: (1) dichloroacetic acid; (2) cyanoacetic acid; (3) chloroacetic acid; (4) 2-chloropropionic acid; (5) 3-chloropropionic acid; (6) acetic acid. ■, Substituted benzoic acids: (1) 3,5-dinitrobenzoic acid; (2) 4-chloro-3-nitrobenzoic acid; (3) 3-nitrobenzoic acid; (4) 4-nitrobenzoic acid; (5) 3,4-dichlorobenzoic acid; (6) 3-chlorobenzoic acid; (7) 4-chlorobenzoic acid; (8) benzoic acid; (9) 4-hydroxybenzoic acid

step, but the results in Figure 2(a) show that the same rates are obtained (at least in relatively strong acid) whether the initial reactant is the free base (2,1,1), and hence $(2,1,1)H^+$ is formed during the reaction, or its monoprotonated derivative.

All available evidence suggests that the second protonation step involves direct entry of the proton into the ligand cavity, to give the di-*endo*-protonated cryptand $(2,1,1)H_2^{2+}$. In an earlier communication [10] we describe the isolation of $(2,1,1)$-H_2^{2+} as its diperchlorate salt under kinetically controlled conditions, and the determination of its *X*-ray structure. The salt, which can be recrystallized unchanged from water, was shown to contain both protons within the ligand cavity, with both nitrogens adopting an *endo*-conformation. The rate of the protonation reaction is also very slow, being several orders of magnitude lower than that expected for protonation of an *exo*-nitrogen or a simple amine by carboxylic acids. The observed rate law and the kinetic hydrogen isotope effects (see below) show direct involvement of HA in the transition state and that proton transfer occurs in the rate-determining step. It may be concluded from the above that the second protonation reaction involves a slow direct proton transfer from acid HA into the ligand cavity.

The difference between (2,1,1) and (1,1,1) is perhaps not entirely surprising. N.m.r. kinetic studies on (1,1,1) and its protonated derivatives [9] have shown that the *endo-endo* conformation is the thermodynamically most stable state for the free ligand and its mono- and di-protonated derivatives, as our work suggests for (2,1,1). However, because of the rigidity of (1,1,1) there is a very high barrier (*ca.* 110 kJ mol⁻¹) to the entry of a proton into the cavity and the alternative reaction of nitrogen inversion and *exo*-protonation occurs more rapidly. Subsequently the more stable internally protonated state is formed, presumably by a deprotonation–inversion–protonation sequence.[9] An analogous set of reaction steps occurs in the formation of the di-*endo*-protonated $(1,1,1)H_2^{2+}$. For the larger and more flexible (2,1,1) ligand, direct entry of the proton into the ligand cavity must be sufficiently easy to be the kinetically dominant reaction, thus preventing the formation as intermediates of significant quantities of the less stable *exo*-protonated species. Some preliminary kinetic results [25] for cryptand (2,2,1) [5] suggest that its kinetic behaviour is similar to that of (2,1,1), but that the protonation rates are significantly higher {for protonation of $(2,2,1)H^+$ by dichloroacetic acid, k_{HA} = *ca.* 2 × 10⁶ mol⁻¹ dm³ s⁻¹; *cf.* $k_{HA}[(2,1,1)H^+]$ = 2.30 × 10⁵ mol⁻¹ dm³ s⁻¹, Table 3}. For (2,2,2),[5] the reaction is rather more complicated. The majority of the conductance change (80—90%) occurs during the mixing time of the apparatus (1—2 ms) but the remainder of the reaction occurs much more slowly. In the presence of excess of acid this slower reaction is independent of the nature and concentration of the acid (k_e *ca.* 3 s⁻¹).[25] The reaction almost certainly involves a conformational change of the ligand.

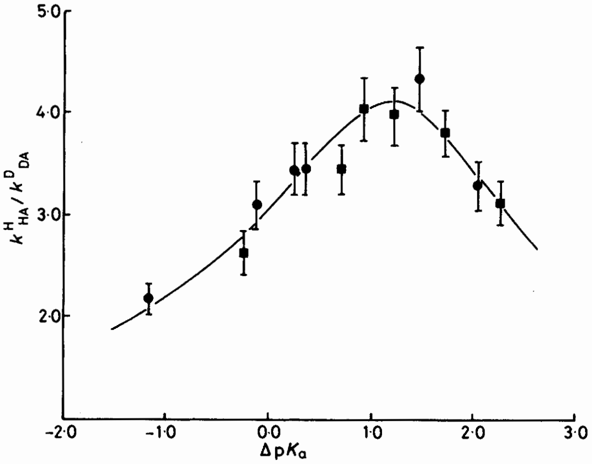

Figure 6. Dependence of kinetic hydrogen isotope effect upon ΔpK_a $\{pK(HA) - pK[(2,1,1)H_2^{2+}]\}$. ●, Substituted acetic acids; ■, substituted benzoic acids

The measured k_{HA} values and isotope effects, $k^H{}_{HA}/k^D{}_{DA}$, for the reaction between the various acids, HA, and $(2,1,1)H^+$ are summarized in Table 7, together with the pK_a values of the acids in methanol. The substituted acetic and benzoic acids show good but separate Brönsted plots (Figure 5) with α values of 0.54 (acetic acids) and 0.49 (benzoic acids). There is no indication of a change in slope from unity to zero around ΔpK [pK(donor) − pK(acceptor)] = 0, characteristic of more reactive systems in which diffusion plays an important role.[2,3] It was suggested earlier [10] that proton transfer in this system is slow because of steric effects and possible non-linear geometry associated with direct entry of the proton into the ligand cavity. Differences in steric interactions are also most likely to be responsible for the separate correlations for the benzoic and acetic acid series.

Figure 6 shows that the isotope effects are quite large and pass through a clear maximum in the vicinity of $\Delta pK = 0$. These isotope effects were necessarily determined using CH_3OD for k^D measurements and so contain solvent isotope effects. These are likely to be small (*i.e.* close to 1) and vary monotonically along the reaction series.[2] The observed effects therefore must have a predominant primary component. The pK range over which k^H/k^D passes through a maximum is quite small and this appears to be due to a change in the isotope effect itself rather than any change in rate-determining step. This behaviour contrasts sharply with that of carbon acids which show much more gradual changes in k^H/k^D with ΔpK.[16] Kresge [1,2] has suggested that reactive systems have transition states whose structures vary more rapidly with ΔpK and isotope effects in such systems consequently should be more sensitive functions of ΔpK. Our results are in agreement with this suggestion. Earlier reports of isotope effects for proton transfer between oxygen and nitrogen bases [2,3] showed similarly sharp changes in k^H/k^D with ΔpK but in these reactions the rate-determining step changes to either encounter or separation within one or two pK units of $\Delta pK = 0$. As these diffusion steps can be expected to show only small isotope effects the observed isotope effects should in any case reduce sharply on either side of $\Delta pK = 0$.

It is particularly interesting that the behaviour of these reactions is in excellent agreement with that predicted on the basis of simple models for proton transfer between centres of comparable basicity: a Brönsted α value close to 0.5 and a maximum isotope effect at ΔpK *ca.* 0.[16] The maximum value observed (k^H/k^D *ca.* 4.3) is, however, significantly below that expected for complete loss in the transition state of zero point energies for stretching vibrations of NH and OH bonds [exp-($E°/298R$) = 8.5 and 10.6, respectively].[16] The relatively low magnitude of k^H/k^D does not appear to be specifically related to any structural feature of the cryptand as a base, as the observed kinetic hydrogen isotope effect for the transfer of a proton from the carbon acid ethyl nitroacetate to $(2,1,1)H^+$ [equation (16)] is $k_1{}^H/k_1{}^D = 8.5$.[26]

$$CH_2(NO_2)CO_2Et + (2,1,1)H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \bar{C}H(NO_2)CO_2Et + (2,1,1)H_2{}^{2+} \quad (16)$$

Finally, the results in different solvents reported in Table 6 and Figure 4 suggest that the same general kinetic behaviour obtains in the various solvents, *i.e.* a rate-determining proton transfer from HA to $(2,1,1)H^+$. In the aprotic solvents there is some deviation from linearity in the plots of k_e against acid concentration at higher concentrations (Figure 4) but this could be due to hydrogen-bonded association between the DCA molecules. It is difficult to interpret in detail the differences between the rates in the various solvents. However, the k_{HA} values in methanol and ethanol are significantly higher than those in the three aprotic solvents. The higher rates may be due to stabilization by hydrogen-bonding of the developing negative charge on the dichloroacetate anion being formed during the protonation reaction.

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