Cryptands as Bases in Proton-transfer Reactions. The Rates and Hydrogen Isotope Effects in the Ionization of Ethyl Nitroacetate by Cryptands

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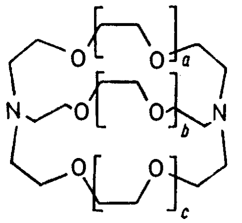
The rates and kinetic hydrogen isotope effects for the proton-transfer reaction between ethyl nitroacetate and three cryptands in the free base and monoprotonated forms have been measured. The catalytic constants for the free bases are *ca.* 1 order of magnitude smaller, and those of the monoprotonated cryptands *ca.* 2 orders of magnitude smaller, than those of ' normal ' bases of comparable basicity. Two possible explanations for the slow rates are discussed: sterically hindered direct transfer of the proton to within the cavity of the ligand, and the reaction of a small, but kinetically active, fraction of molecules containing the free nitrogen atom in an *exo*-conformation. It is argued that the catalytic activity of the unprotonated cryptands is mainly due to the direct transfer of the proton to the cavity, but it is difficult to decide between the two possibilities for the monoprotonated cryptands. The observed kinetic hydrogen isotope effects were 7.2 for the unprotonated cryptand and in the range 8—8.5 for the monoprotonated cryptands.

MOST of the recent interest in macrobicyclic ligands of the type (1)—(3) (cryptands, Cry) [1] has centred on their ability to form stable and highly specific complexes with alkali and alkaline-earth cations (cryptates). A number of studies concerning the thermodynamics [2-5] and kinetics [6-13] of cryptate formation have appeared in the past few years.



(1) $a = b = 0;\ c = 1$ (2,1,1)
(2) $a = 0;\ b = c = 1$ (2,2,1)
(3) $a = b = c = 1$ (2,2,2)

Cryptands are, however, also strong bases, and may exist as monoprotonated and diprotonated derivatives.[2,4] We have recently studied the kinetics of the protolysis of several cryptands in basic aqueous solution, using a pressure-jump relaxation technique.[14] Proton transfer from within the cavity of the monoprotonated form to hydroxide ion was in all cases relatively slow, with observed rate constants varying between 1×10^3 mol^{-1} dm^3 s^{-1} for (1) and 1×10^7 mol^{-1} dm^3 s^{-1} for (3). The results were discussed in relation to possible conformational effects associated with inversion of the nitrogen atoms. Cheney and Lehn [15] have reported that the doubly protonated derivative of the smaller cryptand (1,1,1) reacts only slowly with 5M-KOH.

Here we report results obtained for the rates of the proton-transfer reaction between ethyl nitroacetate and the unprotonated and monoprotonated cryptands (1)—(3). Kinetic hydrogen isotope effects for some of the reactions are also reported. Ethyl nitroacetate was chosen as a substrate because the strong absorbance of its anion means that the reactions can be conveniently followed spectrophotometrically and, in addition, a considerable number of results on the rates of proton transfer from ethyl nitroacetate to a variety of bases of widely varying basicity are available from the work of Bell and his co-workers.[16,17] Their results show a close relationship between the catalytic power and the basic strength over a range of *ca.* 10 powers of 10.

EXPERIMENTAL

Ethyl nitroacetate was prepared by converting ethyl acetoacetate to its α-nitroso-derivative, which was oxidized with sodium dichromate and sulphuric acid.[18] It was purified by distillation under reduced pressure, and according to its n.m.r. spectrum contained $<1\%$ of impurities. Its deuteriated form was prepared by allowing solutions in deuterium oxide to stand long enough to give $>99\%$ deuteriation [$CD_2(NO_2)\cdot CO_2Et$], as judged from its known rate of ionization ($t_{\frac{1}{2}}$ ~40 s).[17] In most of the kinetic experiments with the deuteriated material the reaction was started by adding a small volume of the solution in deuterium oxide to a much greater volume of a solution in ordinary water of the remaining reactants: thus the reaction took place in a medium which was at least 98% H_2O. The procedure was not possible when using the stopped-flow spectrophotometer, which required the mixing of equal volumes of solutions. Two sets of measurements were therefore carried out: in the first set a solution of substrate in H_2O was mixed with the other reactants in D_2O, while in the second set a solution of substrate in D_2O was mixed with a solution of the other reactants in H_2O. In this way the rates of ionization of the C–H and the C–D compounds could be measured in the same solvent, *i.e.* water containing 50 mol % of deuterium.

Triethylamine was purified by distillation. The cryptands (1)—(3) were commercial samples (Merck) used without further purification. The purity of these samples has been checked earlier.[14] Tetraethylammonium perchlorate was prepared from perchloric acid (60% aqueous solution) and tetraethyl ammonium hydroxide (25% aqueous solution), and was purified by recrystallization from water.

The rates of ionization of ethyl nitroacetate were followed by observing the formation of anion directly. The anion absorbs strongly at *ca.* 300 nm. The faster reactions [NEt_3, (2), and (3) as bases] were followed with a Durrum–Gibbs stopped-flow spectrophotometer and the others [(1)H^+, (2)H^+, and (3)H^+ as bases] were followed with a Gilford 2400S spectrophotometer. All kinetic measurements were made at 25 °C. Individual rate constants were reproducible to within 2% except for some faster reactions studied with the stopped-flow where a scatter of 5% was observed.

RESULTS

The reaction between ethyl nitroacetate (SH) and the various bases (B) may be represented by equation (1). In practice, the reaction conditions were such that the equilibrium position corresponded to at least 98% ionization, so

$$SH + B \underset{k_{BH^+}}{\overset{k_B}{\rightleftharpoons}} S^- + BH^+ \qquad (1)$$

that the reverse reaction could be ignored. This was particularly important when the deuteriated form (SD) was studied in ordinary water, since the reverse reaction would lead to the replacement of deuterium by hydrogen. The concentrations of the bases (*ca.* 10^{-3} to 2×10^{-2}M) were considerably higher than that of the substrate (*ca.* 2×10^{-5}M), and under these conditions the rate law shown in equations (2) and (3), is obeyed. For a given series of experiments in which k_e was measured as a function of the

$$-d[S^-]/dt = k_e[S^-] \qquad (2)$$

$$k_e = k_{OH}[OH^-] + k_B[B] \qquad (3)$$

concentration of B, the buffer ratio $[BH^+]/[B]$ was held constant. The ionic strength was also maintained at a constant value by the addition of NEt_4ClO_4, so that the concentration of hydroxide did not vary. The particular conditions under which the reactions were carried out are discussed separately below for triethylamine and each of the three cryptands.

NEt_3. Triethylamine concentrations varied between 7×10^{-4}M and 5×10^{-3}M, with the buffer ratio $r = [BH^+]/[B] = 7.2$. The results are listed in Table 1.

TABLE 1

Rates of reaction of ethyl nitroacetate with triethylamine in water at 25 °C

$10^3[Et_3N]$ [a]/mol dm^{-3}	0.75	1.66	2.48	3.31	4.14
k_e/s^{-1}	56	103	148	174	213
k(calc.)/s^{-1}	59	101	140	178	217

[a] Buffer ratio, $[Et_3NH^+]/[Et_3N] = 7.2$. Ionic strength maintained at 0.03M by addition of Et_3NClO_4. [b] Rate constants calculated from $k_e(\text{calc.}) = 24 \pm 4.67 \times 10^4[Et_3N]$.

Also listed are values calculated from equation (3), with $k_{OH}[OH] = 26(\pm 3)$ s^{-1} and $k_B = 4.7 \times 10^4$ mol^{-1} dm^3 s^{-1}. The hydroxide ion concentration in these solutions may be estimated from equation (4), in which K_w represents the

$$[OH^-] = K_w/rK_a y_\pm^2 \qquad (4)$$

ionic product of water, K_a the acidity constant of Et_3NH^+ ($pK_a = 10.87$),[19] and $y_\pm$ the activity coefficient referred to infinite dilution in water [$y_\pm = 0.850$ at $I = 0.03$ (Table 1) as calculated from the Davies equation[20]]. Thus it was found that the above value of $k_{OH}[OH]$ corresponds to $k_{OH} = 1.8\ (\pm 0.2) \times 10^5$ mol^{-1} dm^3 s^{-1}, which may be compared with an earlier value of $k_{OH} = 1.5 \times 10^{-5}$ mol^{-1} dm^3 s^{-1}, determined in a similar manner from measurements in lutidine and phenol buffers.[17] Similar values for k_{OH} were also obtained from the measurements in the other buffer systems studied here.

Cryptand (3)(2,2,2). The presence of the two nitrogen atoms in the cryptands means that both the free cryptand and its monoprotonated form may act as bases in the proton transfer reactions. Catalytic constants, k_B, and kinetic hydrogen isotope effects, k_B^H/k_B^D, for both forms have been measured, those for (3) in $(3)/(3)H^+$ buffers and those for $(3)H^+$ in $(3)H^+/(3)H_2^{2+}$ buffers. The results are listed in Table 2. Isotope effects for the cryptand (3) were measured in 50% D_2O–H_2O as described above. The catalytic constants were found to be very similar in water ($k_B^H = 4.96 \times 10^3$ mol^{-1} dm^3 s^{-1}) and in 50% H_2O–D_2O ($k_B^H = 4.58 \times 10^3$ mol^{-1} dm^3 s^{-1}), in agreement with earlier findings for pyridine bases.[17]

TABLE 2

Rates of reaction of ethyl nitroacetate and ethyl nitro-[$^2H_2$]acetate with the cryptand (3) and its monoprotonated derivative at 25 °C

(i) Cryptand (3) with $CH_2(NO_2)CO_2Et$–solvent H_2O					
$10^3[(3)]$ [a]/mol dm^{-3}	0.94	1.87	2.81	3.74	4.68
k_e/s^{-1}	15.7	20.2	25.9	28.9	34.2
k(calc.) [b]/s^{-1}	15.7	20.3	24.9	29.6	34.2
(ii) Cryptand (3) with $CH_2(NO_2)CO_2Et$–solvent 50% D_2O–H_2O					
$10^3[(3)]$ [c]/mol dm^{-3}	0.99	1.98	2.97	3.96	4.96
k_e^H/s^{-1}	11.7	17.3	21.6	24.7	30.2
k^H(calc.) [d]/s^{-1}	12.3	16.9	21.4	25.9	30.5
(iii) Cryptand (3) with $CD_2(NO_2)CO_2Et$–solvent 50% D_2O–H_2O					
$10^3[(3)]$ [e]/mol dm^{-3}	1.02	2.04	3.06	4.08	5.10
k_e^D/s^{-1}	1.65	2.40	2.96	3.55	4.35
k^D(calc.) [f]/s^{-1}	1.68	2.34	2.99	3.64	4.29
(iv) Cryptand $(3)H^+$ with $CH_2(NO_2)CO_2Et$–solvent H_2O					
$10^3[(3)H^+]$ [g]/mol dm^{-3}	0.919	1.84	2.76	3.68	4.60
$10k_e^H/s^{-1}$	1.05	1.55	2.09	2.48	2.93
$10k^H$(calc.) [h]/s^{-1}	1.07	1.54	2.01	2.41	2.95
(v) Cryptand $(3)H^+$ with $CD_2(NO_2)CO_2Et$–solvent H_2O					
$10^3[(3)H^+]$ [g]/mol dm^{-3}	0.919	1.84	2.76	3.68	4.60
$10^2k_e^D/s^{-1}$	1.78	2.42	3.03	3.45	4.07
10^2k^D(calc.) [i]/s^{-1}	1.81	2.38	2.95	3.52	4.09

[a] $[(3)H^+]/[(3)] = 2.02$, ionic strength = 0.01M–(NEt_4ClO_4). [b] $k(\text{calc.}) = 11.0 + 4.96 \times 10^3\ [(3)]$. [c] $[(3H^+]/[(3)] = 2.02$, ionic strength = 0.01M–(NEt_4ClO_4). [d] $k_e^H(\text{calc.}) = 7.8 + 4.58 \times 10^4\ [(3)]$. [e] $[(3)H^+]/[(3)] = 3.92$, ionic strength = 0.02M–(NEt_4ClO_4). [f] $k^D(\text{calc.}) = 1.03 + 6.4 \times 10^3\ [(3)]$. [g] $[(3)H_2^{2+}]/[(3)H^+] = 1.03$, ionic strength = 0.019M–(NEt_4ClO_4). [h] $k^H(\text{calc.}) = 0.06 + 51.0\ [(3)H^+]$, see text. [i] $k^D(\text{calc.}) = 0.0124 + 6.2\ [(3)H^+]$, see text.

The catalytic constant of (3) was considerably larger than that of $(3)H^+$ so that catalysis by the latter could be ignored in the $(3)/(3)H^+$ buffers. However, in the $(3)H^+/(3)H_2^{2+}$ buffers used to determine k_B for $(3)H^+$, the contribution to the rate from the small concentration of (3) in equilibrium was significant. Thus slopes of k_e against $[(3)H^+]$ for $[(3)H^+]/[(3)H_2^{2+}] = 3.3$, 0.97, and 0.53 were 84.5, 51.0, and 46.5 mol^{-1} dm^3 s^{-1} respectively. Extrapolation to zero ratio leads to $k_B[(3)H^+] = 38.5$ mol^{-1} dm^3 s^{-1}. Detailed results for this system when $[(3)H^+]/[(3)H_2^{2+}] = 0.97$, at which the ionization of the deuteriated ethyl nitroacetate was studied, are given in Table 2. The observed isotope effect in this system can be readily corrected to allow for the contribution from (3), using the measured isotope effect for catalysis by (3). The isotope effect was not measured at lower values of $[(3)H^+]/[(3)H_2^{2+}]$ because the reversibility of reaction (1) at lower pH values would result in hydrogen exchange occurring during the reactions.

Cryptand (2)(2,2,1). The catalytic constant for (2) and the catalytic constants and kinetic hydrogen isotope effects for $(2)H^+$ were measured. The results are listed in Table 3. There was again some contribution from the free base in the $(2)H^+/(2)H_2^{2+}$ buffers used to determine $k_B[(2)H^+]$. The effect, however, was considerably smaller than for (3), because of the much wider gap in the pK_a values for the doubly and monoprotonated forms of (2).[2,14] The slopes of k_e *vs.* $[(2)H^+]$ for ratios of 2.23 and 0.98 were 20.1 and 18.2 mol^{-1} dm^3 s^{-1} respectively, leading to a value of $k_B[(2)H^+]$ = 16.7 mol^{-1} dm^3 s^{-1}. Isotope effects were determined in solutions containing $[(2)H^+]/[(2)H_2^{2+}]$ = 0.98 and are uncorrected for the small contributions from the free cryptand (2).

Cryptand (1)(2,1,1). The catalytic constant and kinetic hydrogen isotope effects were measured for the monoprotonated derivative of (1). The results are listed in Table 4. There was no evidence of a significant contribution to the rate by the free cryptand (1) in the buffers studied. The slopes of k_e against $[(1)H^+]$ were the same, within experimental error, for $[(1)H^+]/[(1)H_2^{2+}]$ = 0.73 and 0.42.

TABLE 3

Rates of reaction of ethyl nitroacetate and ethyl nitro-[$^2H_2$]acetate with the cryptand (2) and its monoprotonated derivative in water at 25 °C

(i) Cryptand (2) with $CH_2(NO_2)CO_2Et$					
$10^3[(1)]$ [a]/mol dm^{-3}	0.763	1.53	2.29	3.05	3.82
k_e/s^{-1}	28.8	35.2	38.7	42.2	47.3
k(calc.) [b]/s^{-1}	30.0	34.3	38.6	42.9	47.2
(ii) Cryptand $(2)H^+$ with $CH_2(NO_2)CO_2Et$					
$10^3[(2)H^+)]$ [c]/mol dm^{-3}	1.85	3.70	5.55	7.40	9.25
$10k_e^H$/s^{-1}	1.45	1.71	2.09	2.42	2.78
$10k^H$(calc.) [d]/s^{-1}	1.42	1.75	2.09	2.43	2.76
(iii) $(2)H^+$ with $CD_2(NO_2)CO_2Et$					
$10^3[(2)H^+]$ [c]/mol dm^{-3}	1.85	3.70	5.55	7.40	9.25
$10^2k_e^D$/s^{-1}	2.73	3.19	3.61	3.97	4.46
10^2k^D(calc.) [e]/s^{-1}	2.77	3.18	3.60	4.02	4.43

[a] $[(2)H^+]/[(2)]$ = 8.8, ionic strength = 0.035M–(NEt_4ClO_4). [b] (k(calc.) = 25.7 + 5.63 × 10^3 [(2)]. [c] $[(2)H_2^{2+}]/[(2)H^+]$ = 1.02, ionic strength = 0.038M–(NEt_4ClO_4). [d] k^H(calc.) = 0.108 + 18.2 $[(2)H^+]$, see text. [e] k^D(calc.) = 0.0235 + 2.25 $[(2)H^+]$. see text.

TABLE 4

Rates of reaction of ethyl nitroacetate and ethyl nitro-[$^2H_2$]acetate with the monoprotonated cryptand (1) in water at 25 °C

(i) Cryptand $(1)H^+$ with $CH_2(NO_2)CO_2Et$					
$10^3[(1)H^+]$ [a]/mol dm^{-3}	4.06	8.13	12.2	16.3	20.3
$10k_e^H$/s^{-1}	4.42	4.99	5.53	6.13	6.66
$10k_e^H$(calc.)[b]/s^{-1}	4.41	4.98	5.54	6.12	6.67
(ii) $(1)H^+$ with $CD_2(NO_2)CO_2Et$					
$10^3[(1)H^+]$ [a]/mol dm^{-3}	4.06	8.13	12.2	16.3	20.3
$10^2k_e^D$/s^{-1}	8.88	9.50	9.83	11.0	11.4
$10^2k_e^D$(calc.) [c]/s^{-1}	8.76	9.43	10.1	10.8	11.4

[a] $[(1)H_2^{2+}]/(1)H^+]$ = 1.37, ionic strength = 0.11M–(NEt_4ClO_4). [b] k_e^H(calc.) = 0.385 + 13.9 $[(1)H^+]$. [c] k_e^D(calc.) 0.081 + 1.63 $[(1)H^+]$.

TABLE 5

Catalytic constants and kinetic hydrogen isotope effects for the ionization of ethyl nitroacetate at 25 °C

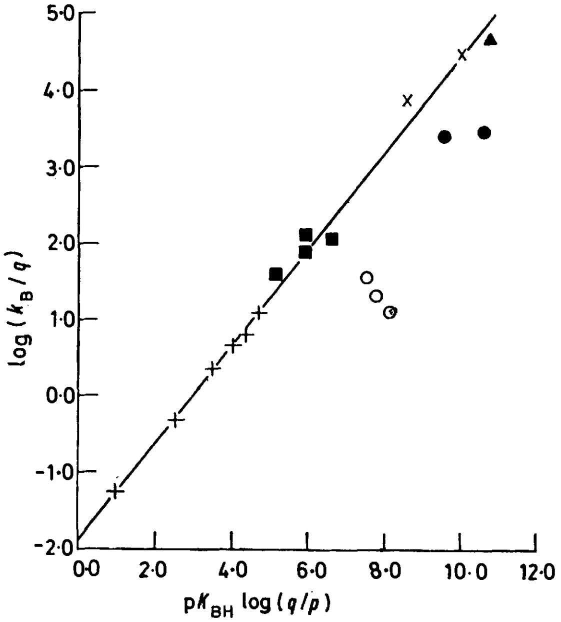
Base (B)	pK_{BH^+}	k_B^H/mol^{-1} dm^3 s^{-1}	k_B^H/k_B^D
$(3)H^+$	7.3 [a]	38.5	8.4
$(2)H^+$	7.5 [a]	16.7	8.1
$(1)H^+$	7.9 [a]	13.9	8.5
(3)	9.8 [b]	4.6 × 10^3	7.2
(2)	10.9 [b]	5.6 × 10^3	
Et_3N	10.9 [c]	4.7 × 10^4	

[a] Ref. 2. [b] Ref. 14. [c] Ref. 19.

The catalytic constants and isotope effects for all the systems studied are summarized in Table 5. In addition to the results given, it is possible to obtain values of k_{OH}^H/k_{OHD} from the intercepts of the various plots of k_e against [B]. These give a value of $k_{OH}^H/k_{OH}^D = 4.6 \pm 0.2$, in good agreement with the value of 4.6 reported by Barnes and Bell.[17]

DISCUSSION

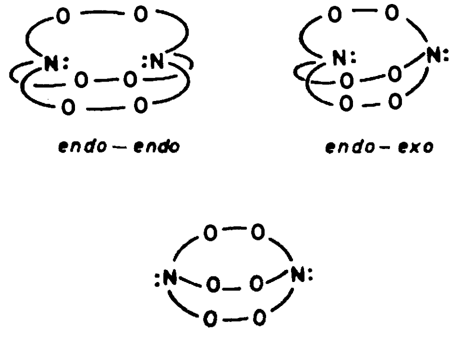
It is clear from the dependence of the ionization rate on the cryptand concentration, and the large kinetic hydrogen isotope effects, that proton transfer occurs directly from the substrate to the cryptand. A comparison of the observed catalytic constants with those previously found for other bases, however, shows that the cryptands are somewhat less effective as catalysts than other bases of comparable thermodynamic basicity. The Figure, which includes the results of Bell and his co-workers,[16,17] shows a plot of log (k_B/q) against pK_{BH^+} — log (q/p), where p and q are statistical corrections to allow for the number of equivalent acidic sites on BH^+ and the number of equivalent basic sites on B respectively.[21] With the exception of the cryptands, the remaining bases, including carboxylate anions, substituted pyridines, phenoxides, and triethylamine, show a good correlation between reaction rate and basic strength. The negative deviation of the points corresponding to the monoprotonated cryptands is particularly marked.



Dependence of the rate of ionization of ethyl nitroacetate upon the strength of the reacting base: (+) carboxylate anions (ref. 16); (■) substituted pyridines (ref. 16, 17); (×) phenoxide ions (ref. 17); (▲) triethylamine; (○) monoprotonated cryptands, $(1)H^+$, $(2)H^+$, and $(3)H^+$f rom left to right; (●) cryptands (3) (left) and (2)

Factors causing negative deviations from Brönsted relations (see Figure) have been discussed in some detail,[21] but two may be singled out as being particularly relevant to the present results. The first is the presence of appreciable steric hindrance to proton transfer. The transfer of a proton directly to or from the cavity of the cryptands would presumably be subject to considerable steric constraints, and this could account for the relatively slow rates observed, *i.e. ca.* 2 orders of magnitude slower than 'ordinary' bases of comparable basicity for the monoprotonated cryptands, and *ca.* 1 order of magnitude slower for the free cryptands.

A second factor which can cause deviations from the Brönsted relation is the involvement of subsidiary equilibria (in addition to the gain or loss of a proton) in the equilibrium used to define the basic strength of the catalyst (*e.g.* the lactol-keto-acid equilibria of keto-acids).[21,22] In the present case, there seems little doubt from the slow rates of proton transfer to hydroxide ions [14,15] and by analogy with metal cryptates,[1,2] that the thermodynamically stable form of the protonated cryptands is that containing the proton in the cavity of the ligands, with both nitrogens having the *endo*-conformation. However, because of the possibility of nitrogen inversions, the cryptands may exist in three forms (see Scheme): *exo-exo, endo-exo,* and *endo-endo.*


endo — endo

endo — exo

exo — exo

SCHEME

It is possible then that one or other of the *exo* forms is the kinetically active species, with rate-determining proton transfer occurring from ethyl nitroacetate to an *exo*-nitrogen, followed by a rapid re-equilibration to give the thermodynamically favoured form of the resulting mono- or di-protonated cryptand.

Our results may be used to estimate an upper limit to the equilibrium concentrations of *exo*-forms in the free and monoprotonated cryptands. Considering firstly the monoprotonated cryptands as bases, the results in Table 5 show that the k_B values are $<10^{-3}$ of that for triethylamine. Assuming that the reactivity of a free *exo*-nitrogen in a monoprotonated cryptand with an *exo-exo* conformation would be very similar to that of a normal tertiary amine, these results suggest that a maximum of *ca.* 1 in 10^3 of monoprotonated cryptand molecules have an *exo-exo* conformation. The basicity of a free *exo*-nitrogen in a monoprotonated *exo-endo*-cryptand would be expected to be reduced by the presence of the positive charge on the *endo* NH^+ group but should be between that of a normal tertiary amine and the observed thermodynamic basicity of the monoprotonated cryptand. Thus it may be estimated from the Figure that a maximum of *ca.* 0.2—0.5% of molecules having such conformations may be present.

Similarly, the observed rates for the free cryptands could be accounted for by the presence of *ca.* 10% of *exo*-nitrogens if those in *endo*-conformations are kinetically inactive. It is likely, however, that the proportion of free cryptands containing *exo*-nitrogens is very much lower than this figure. The overall basicities of the free cryptands are very similar to those of normal tertiary amines, so that the proportions of free cryptands with *exo*-nitrogens should be closely reflected in those of the monoprotonated forms, *i.e.* less than 0.1% for *exo-exo* and 0.5% for *exo-endo*. The catalytic activity of the unprotonated cryptands then appears to be mainly due to the direct transfer of the proton into the ligand cavity. It is more difficult to decide whether the results obtained for the monoprotonated cryptands represent the rate of transfer to within the cavity, or simply the reaction of a very small, but kinetically active, fraction of molecules with free nitrogens in the *exo*-conformation.

Finally, it may be noted that the observed kinetic hydrogen isotope effects, whilst confirming that proton transfer occurs directly from the substrate to the cryptands, do not show any unusual features. Results obtained previously for proton transfer from ethyl nitroacetate show a maximum in k^H/k^D for bases with pK_{BH^+} *ca.* 6. Values of k^H/k^D were *ca.* 6—7 for carboxylate anions, 9—10 for substituted pyridines, and 7—8 for phenoxide ions. These may be compared with the present values of 7.2 for the cryptand (3) and 8—8.5 for the monoprotonated cryptands.

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