

## The Occurrence of an Hydride Shift in the Aromatisation of 1,4-Epoxy-1,4-dihydronaphthalenes

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The acid-catalysed aromatisation of [1,4-<sup>2</sup>H<sub>2</sub>]-1,4-epoxy-1,4-dihydronaphthalene and [4-<sup>2</sup>H]-1,4-epoxy-1-methyl-1,4-dihydronaphthalene is shown to result in partial retention of deuterium at the 2-position of 1-naphthol and 4-methyl-1-naphthol, respectively.

1,4-Epoxy-1,4-dihydronaphthalene is aromatised to 1-naphthol in the presence of acid catalyst.<sup>1</sup> The 1,4-dimethyl derivative (1) with aqueous hydrochloric acid is isomerised to the 2-naphthol (3), in which the hydroxy-group is derived from solvent water;<sup>2</sup> similarly, with methanolic HCl (1) gives mainly the 2-naphthyl ether (4), although 1,4-epoxy-1,2,3,4-tetramethyl-1,4-dihydronaphthalene (2) affords the products (5) and (6) by substitution into a methyl group.<sup>3</sup> However, under the non-nucleophilic conditions of catalysis by boron trifluoride in dry benzene, the aromatisation of compound (1) is accompanied by a 1,2-shift of a methyl group to give the 1-naphthol (7).<sup>2</sup> A similar rearrangement occurs in trifluoroacetic acid with the 7-oxabicyclo[2.2.1]heptadiene derivatives (8) and (9) to give a phenolic product and the cyclohexadienone (10), respectively.<sup>4</sup>

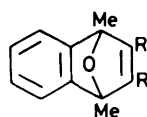
Therefore we were led to investigate the acid-catalysed rearrangement of the isotopically labelled 1,4-oxides (15) and (19), expecting, on analogy with 1,2-epoxy-1,2-dihydronaphthalene (11),<sup>5</sup> to find the occurrence of an NIH shift,<sup>6</sup> whereby the product 1-naphthol would contain more or less deuterium at its 2-position. Previous workers had compared the ratio of aromatic products (13):(14) obtained from the 1,4-oxides (12a and b) on treatment with hot ethanol saturated with anhydrous HCl, but their labelled compound (12b) was of low isotopic purity and they did not report the extent, if any, of deuterium retention at the 2-position of the 1-naphthol (13).<sup>7</sup>

### Experimental

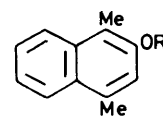
<sup>1</sup>H N.m.r. spectra were obtained at 60 MHz (Perkin-Elmer R10, and Varian A-60A and EM360-A spectrometers) for solutions in [<sup>2</sup>H]chloroform or carbon tetrachloride. U.v. spectra were recorded using Pye-Unicam SP800 and SP8-500 instruments. Ether refers to diethyl ether, and light petroleum to the fraction boiling between 40–60 °C.

[1,4-<sup>2</sup>H<sub>2</sub>]-1,4-Epoxy-1,4-dihydronaphthalene (15).—The method of Ziegler<sup>8</sup> to prepare [2,5-<sup>2</sup>H<sub>2</sub>]furan was modified by the use of an excess of butyl-lithium (1.0 mol) to furan (0.2 mol) and by evaporating to dryness, thereby removing ether with any unmetallated furan, before replacing the ether solvent and quenching the dilithiofuran with deuterium oxide. The mixture was then distilled through a Vigreux column, and the fraction boiling below 35 °C collected; this contained the [2,5-<sup>2</sup>H<sub>2</sub>]furan (singlet n.m.r. absorption for 3- and 4-H, and no absorption for 2- and 5-H) in ether.

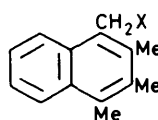
Isopentyl nitrite (27 ml, 0.2 mol) was added to the total [2,5-<sup>2</sup>H<sub>2</sub>]furan in ether and this mixture added dropwise in parallel with anthranilic acid (24 g, 0.175 mol) in 1,2-dimethoxyethane (200 ml) into a flask containing 1,2-dimethoxyethane (100 ml), which was stirred and maintained at 75 °C. The addition was interrupted at intervals and the volume reduced by allowing ether to distil out. Finally the mixture was refluxed for 0.5 h, and then poured into aqueous sodium hydroxide (30 g NaOH in 500



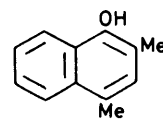
(1) R = H  
(2) R = Me



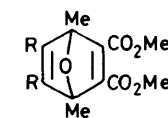
(3) R = H  
(4) R = Me



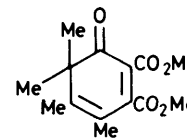
(5) X = Cl  
(6) X = OMe



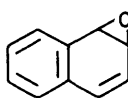
(7)



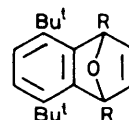
(8) R = H  
(9) R = Me



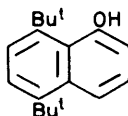
(10)



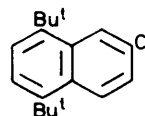
(11)



(12) a; R = H  
b; R = D



(13)



(14)

ml). The aqueous mixture was distilled until the vapour temperature reached 95 °C. The residue was cooled and extracted repeatedly with chloroform; the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to a red oil, which was redissolved in light petroleum and chilled to produce crystals. Recrystallisation from light petroleum afforded the 1,4-oxide (15) (8.0 g), m.p. 54.5–55.5 °C after sublimation (lit.,<sup>1</sup> 55–56 °C), containing 99% 1,4-<sup>2</sup>H<sub>2</sub> (<sup>1</sup>H n.m.r. spectrum).

[4-<sup>2</sup>H]-1,4-Epoxy-1-methyl-1,4-dihydronaphthalene (19).—A stirred suspension of 2-chloromercurio-5-methylfuran<sup>9</sup> (60 g) in [<sup>2</sup>H<sub>2</sub>]water (90 ml) containing also sodium chloride (11 g) and oleum (4.6 ml) was heated under a short fractional distillation column and [5-<sup>2</sup>H]-2-methylfuran collected continuously, b.p. 62–64 °C (yield 10.3 g), 93% <sup>5-<sup>2</sup>H</sup> (n.m.r. spectrum).<sup>10</sup>

Anthranilic acid (11 g) was converted into benzenediazonium 2-carboxylate,<sup>11</sup> which was added as a slurry in tetrahydrofuran in portions over 45 min to [5-<sup>2</sup>H]-2-methylfuran (5.0 g) in tetrahydrofuran (100 ml) heated under reflux during the addition and for a further 30 min. The solution was cooled, diluted with water, and extracted with light petroleum; the extract was washed twice with 1% aqueous sodium hydroxide, then with water, and dried (MgSO<sub>4</sub>). After removal of the light petroleum, the residue was distilled to give the 1,4-oxide (19) (5.0 g), b.p. 48.5–50 °C at 0.25 mmHg (lit.,<sup>12</sup> 57–59 °C at 0.2 mmHg), 93% <sup>4-<sup>2</sup>H</sup> (from comparison of intensities of the n.m.r. signals for 4-H and the CH<sub>3</sub> group).

*Aromatisation of [1,4-<sup>2</sup>H<sub>2</sub>]-1,4-Epoxy-1,4-dihydronaphthalene (15).*—Since the 1,4-oxide (15) does not absorb above 290 nm, the increase in absorption at 323 nm (a shoulder in the u.v. absorption of 1-naphthol) provides a direct measure of the formation of aromatic products (16a + b). The 1,4-oxide (15) (6 mg) was added to methanol (25 ml) containing concentrated hydrochloric acid (250 μl) at 50.5 °C. The temperature was maintained constant and the u.v. absorption of the solution recorded at intervals. The reaction followed pseudo-first-order kinetics to at least 90% completion; log  $A_{\infty}/(A_{\infty} - A_t)$  was plotted against time, and the rate constant found from the slope of this line.

In separate experiments for isolation of the 1-naphthol product (16a + b), the 1,4-oxide (15) (66 mg) was added to methanol (100 ml) containing concentrated hydrochloric acid (1.00 ml), preheated to 50.5 °C. The mixture was swirled and maintained at 50.5 °C for 15 or 100 min, respectively; the reaction was then quenched by rapid addition of 2M aqueous sodium hydroxide (6 ml) and cooling in ice. Methanol was evaporated at 0.1 mmHg pressure, and the residue was redissolved in 2M-sodium hydroxide (4 ml) and water (10 ml). This solution was extracted with ether (2 × 25 ml) and the aqueous layer cooled to 0 °C, acidified with 2M-hydrochloric acid (12 ml), and again extracted with ether (2 × 25 ml). The ether extract was dried (Na<sub>2</sub>SO<sub>4</sub>) at 0 °C for 30 min; the ether was evaporated, and the residue recrystallised from light petroleum. The extent of incorporation of deuterium in the 2-position was determined by integration of the signal for 2-H versus those for 5-H and 8-H in the <sup>1</sup>H n.m.r. spectrum.<sup>13</sup>

*Deuteration and Dedeuteration of 1-Naphthol.*—Freshly recrystallised and sublimed 1-naphthol (35 mg) was dissolved in [O-<sup>2</sup>H]methanol, and the solution evaporated to dryness. The residue was redissolved in [O-<sup>2</sup>H]methanol (0.5 ml) to which was added concentrated hydrochloric acid (5.0 μl). The mixture was maintained at 50.5 °C and the <sup>1</sup>H n.m.r. spectrum recorded at intervals, until after 6 h the high-field absorption<sup>13</sup> for 2-H had disappeared. The solution was then evaporated to dryness, and evaporated again after addition of acetone (0.2 ml). The residue of [2, O-<sup>2</sup>H<sub>2</sub>]-1-naphthol (which also contained undetermined amounts of deuterium at the 3- and 4-positions) was redissolved in methanol (0.5 ml) and heated to 50.5 °C. 11M-Hydrochloric acid (5.0 μl) was added and the progress of reaction at 50.5 °C followed by n.m.r. spectrometry; the relative intensities of absorptions for 2-H and 8-H measured the formation of (16b) and the total (16a + b), respectively. Five values of log (16a + b)/(16a) were plotted against time, and the rate constant determined from the slope of this line.

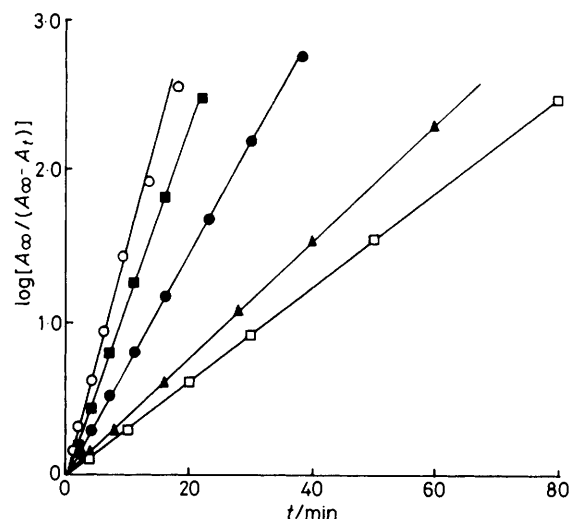


Figure 1. Plots to show first-order kinetics for aromatisation of the 1,4-oxide (19) at 25 °C in methanol with different HCl concentrations: ○ 0.11M, ■ 0.055M, ● 0.027M, ▲ 0.011M, □ 0.009M

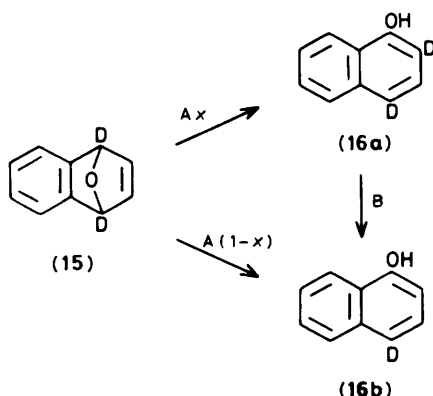
*Aromatisation of [4-<sup>2</sup>H]-1,4-Dihydro-1-methylnaphthalene (19).*—Concentrated hydrochloric acid was diluted with methanol to make solutions of known concentration within the range 0.009–0.11M. Kinetics of the rearrangement of the 1,4-oxide (19) at 25 °C were followed by addition of samples of (19) (2 mg) separately to 25 ml of each concentration of methanolic HCl in turn and recording the increase in u.v. absorption at 312 or 326 nm (shoulders on the longest wavelength band,  $\lambda_{\max}$  302 nm); the results are shown in Figure 1. The same reaction was also followed u.v.-spectrophotometrically at 50.5 °C, under the same conditions as for the 1,4-oxide (15).

In separate experiments for isolation of the product (22), the 1,4-oxide (19) (0.20 g) was added to methanol (100 ml) containing concentrated hydrochloric acid (0.10 ml). The solution was kept at 25 °C for 2 h, then added to saturated aqueous sodium hydrogen carbonate (0.4 ml) and water. Methanol was removed by rotary evaporation, and the aqueous residue was extracted with ether; the ether extract was washed with water, dried (MgSO<sub>4</sub>), and the ether evaporated. The residue was recrystallised from light petroleum to give 4-methyl-1-naphthol (22a + b) (80 mg), m.p. 82–84 °C (lit.,<sup>14</sup> 83–84 °C), containing 22.3 ± 1.0% <sup>2-<sup>2</sup>H</sup> [estimated by integration of the n.m.r. signal for 2-H ( $\delta$  6.60, d) versus that for CH<sub>3</sub> ( $\delta$  2.56 s)]. Other samples of the 1,4-oxide (19) were allowed to react for 1 or 3 h and gave the 1-naphthol (22a + b) containing 21.7 and 20.3% deuterium, respectively.

The 1,4-oxide (19) (0.20 g) was added to dry benzene (20 ml) containing boron trifluoride etherate (20 μl). The solution was kept at 25 °C for 20 min, when reaction was quenched by pouring the mixture into saturated aqueous sodium hydrogen carbonate (2 ml) and ice. The product (22a + b) was extracted into ether, the ether extract separated and dried (MgSO<sub>4</sub>), the ether evaporated, and the residue recrystallised from light petroleum to give (22a + b) (125 mg), which contained 67% <sup>2-<sup>2</sup>H</sup> (from integration of the n.m.r. spectrum).

## Results and Discussion

*[1,4-<sup>2</sup>H<sub>2</sub>]-1,4-Epoxy-1,4-dihydronaphthalene (15).*—Preliminary experiments established that more forcing conditions were required for the aromatisation of the 1,4-oxide (15) than the 1,2-oxide (11);<sup>5,15</sup> this is expected, if the rate-determining step in both cases involves opening of the oxide ring, which is more



Scheme 1.

strained in (11) than in (15). Mass spectrometric analysis of the 1-naphthol product from rearrangement of (15) in methanolic HCl at 50 °C showed that [2,4- $^2\text{H}_2$ ]-1-naphthol (16a) was only a small fraction of the total product and that the amount fell with increasing time of reaction as a result of the acid-catalysed exchange (16a)  $\rightarrow$  (16b). The simplest situation is that represented by Scheme 1, in which A denotes the aromatisation and B the exchange reaction. If a quantity  $X$  is defined as that fraction of the product which is found to contain both deuterium atoms, then the value of  $X$  extrapolated to zero time identifies the fraction  $x$  of (15) which reacts with retention of deuterium. The rate of the back reaction (16b)  $\rightarrow$  (16a) is negligible under these conditions, since exchangeable  $^1\text{H}$  far outweighs  $^2\text{H}$ . Nor are we concerned with exchange of  $^1\text{H}$  for  $^2\text{H}$  at the 4-position, since in subsequent experiments we determined only the retention of deuterium at the 2-position. In any case, dedeuteriation probably will occur more slowly from the 4- than from the 2-position, since kinetic data for detritiation of labelled 1-methoxynaphthalene in trifluoroacetic acid<sup>16</sup> indicate that the 4-position is *ca.* 5–6 times less reactive than the 2-position at 70 °C.

Analysis of the reaction kinetics associated with Scheme 1 allows deduction of equations (1) and (2),<sup>17</sup> in which  $k_A$  and  $k_B$  are pseudo-first-order rate constants for reactions A and B, respectively, under fixed conditions of acid concentration and solvent.

$$[(16a)]_t = [(15)]_{t=0} x k_A (e^{-k_A t} - e^{-k_B t}) / (k_B - k_A) \quad (1)$$

$$[(16b)]_t = \frac{[(15)]_{t=0} x (k_A e^{-k_B t} - k_B e^{-k_A t})}{(k_B - k_A) + 1.0 - (1-x)e^{-k_A t}} \quad (2)$$

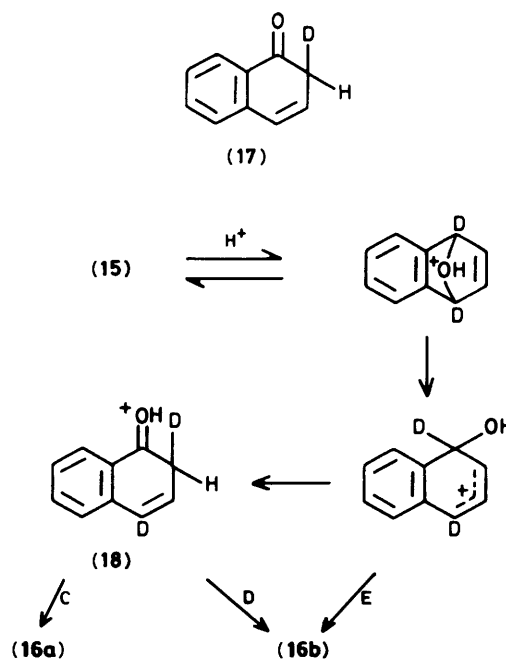
Also, since the quantity  $X_t$  is defined by the ratio  $[(16a)]_t / [(16a) + (16b)]_t$ , it is possible to derive an expression (3) which enables  $x$  to be determined from measurements of  $X_t$ ,  $k_A$ ,  $k_B$ , and  $t$ .

$$X_t = \frac{x k_A (e^{-k_A t} - e^{-k_B t})}{(k_B - k_A)(1 - e^{-k_A t})} \quad (3)$$

The following values of pseudo-first-order rate constants were obtained graphically as described above:  $k_A = 0.0048$  and  $k_B = 0.0054 \text{ min}^{-1}$ .

In addition, analysis of the 1-naphthol (16) isolated after 15 and 100 min gave the following values of  $X$ :  $X_{15} = 0.233 \pm 0.005$  and  $X_{100} = 0.154 \pm 0.005$ .

Equation (3) does not clearly show the variance of  $x$  due to variance in  $k_A$ ,  $k_B$ ,  $X$ , and  $t$ , and nor can  $x$  be expressed accurately as a sum of linear terms in the above variables.



Scheme 2.

Therefore, values of  $X_t$  were calculated for all permutations of these variables, allowing a range of values for each particular variable wide enough to include what could reasonably be expected as a worst case:  $0.004 \leq k_A \leq 0.006 \text{ min}^{-1}$  (5 values);  $0.002 \leq k_B \leq 0.008 \text{ min}^{-1}$  (8 values);  $0.10 \leq x \leq 0.30$  (5 values) and  $t$  took the values 14.5, 15.0, 15.5, 99, 100, and 101 min. The wider range of values for  $k_B$  than for  $k_A$  is due to the use of fewer data points to evaluate  $k_B$ . By a standard multiple regression analysis, a simple function of  $x$  is expressed in simple terms of  $k_A$ ,  $k_B$ ,  $X$ , and  $t$ , and relationship (4) was found to hold over the ranges of values listed above with a correlation coefficient ( $R^2$ ) of 0.996.

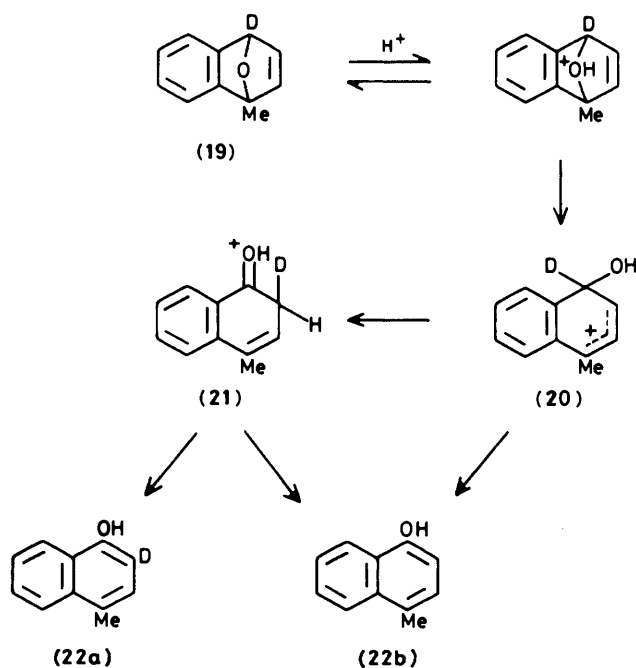
$$X_t/x = 0.9920 - 0.426 k_B t \quad (4)$$

Equation (4) can be rearranged to (5), in which  $\Delta$  indicates the experimental uncertainty in each given variable. The outside limits of uncertainty are 0.5 min at  $t$  15 and 1 min at  $t$  100 min, and *ca.* 10% in the value of  $k_B$ . Hence we calculate values for  $x = 0.24 \pm 0.01$  and  $0.20 \pm 0.02$  (based on the measured values of  $X_t$  at  $t = 15$  and 100 min, respectively).

$$x = \frac{(X_t \pm \Delta X_t)}{0.992 - 0.426 k_B t \pm 0.426(t \Delta k_B \pm k_B \Delta t)} \quad (5)$$

The observation of 80% retention of deuterium at the 2-position of 1-naphthol when the 1,2-oxide (11) labelled with deuterium exclusively at either the 1- or the 2-position is aromatised at pH 7 implies that all of (11) reacts by the NIH shift and that an isotope effect  $k_H/k_D = 4.0$  operates in the tautomerisation of the intermediate (17).<sup>5</sup> If we assume the same isotope effect for aromatisation of the conjugate acid (18) (the ratio of the rate constants for reactions C and D in Scheme 2), then the formation of 24% of (16a) from the 1,4-oxide (15) corresponds to *ca.* 30% of reaction *via* a hydride shift and the intermediate (18), the remaining *ca.* 70% of (15) giving only (16b) by the more direct pathway E.

[4- $^2\text{H}$ ]-1,4-Epoxy-1-methyl-1,4-dihydronaphthalene (19).—Although the above results demonstrate unambiguously a



Scheme 3.

significant involvement of the hydride shift mechanism in the acid-catalysed aromatisation of the 1,4-oxide (15), [4- $^2H$ ]-1,4-epoxy-1-methyl-4-deuterio-1,4-dihydronaphthalene (19) was chosen as a simpler case for further study. The methyl group was expected to cause a marked increase in the rate of aromatisation [if the rate-determining step involves formation of the carbonium ion intermediate (20)] but to have little effect on the rate of dedeuteriation at the 2-position of the product (22a).

Indeed, under the same conditions employed for the aromatisation of the 1,4-oxide (15), compound (19) rearranged *ca.* 400 times faster to give 4-methyl-1-naphthol (22a + b). The aromatisation of (19) was conveniently fast ( $t_{1/2}$  *ca.* 22 min) with only 0.011M-HCl in methanol and at 25 °C rather than 50 °C. Moreover, under these milder conditions the exchange reaction (22a)  $\rightarrow$  (22b) was unimportant, and the fraction of the product (22a)/(22a + b) containing deuterium was found to be nearly independent of the time of reaction.

The mechanism outlined in Scheme 3 for the aromatisation of the 1,4-oxide (19) has a fast, reversible step preceding the rate-determining step. This same feature is characteristic of many enzyme-catalysed reactions, with which are associated the well known Michaelis-Menten kinetics.<sup>18</sup> The effect of varying the acid concentration on the rate of aromatisation of the 1,4-oxide (19) is shown in Figure 1, from which values of the pseudo-first-order rate constant  $k_A$  were derived. A double reciprocal plot of  $1/k_A$  versus  $1/[HCl]$  is linear (Figure 2), from which the intercept on the y-axis gives a limiting value for  $k_A$  (0.21 min<sup>-1</sup>) corresponding to complete protonation of the 1,4-oxide (19). From the slope of the line in Figure 2 the apparent basicity ( $pK_a$  1.3) of the 1,4-oxide (19) in methanol is found to be surprisingly high in relation to the basicity of simple ethers, which implies that the reaction mechanism may be more complicated than that represented in Scheme 3.

The extent of retention of deuterium in 4-methyl-1-naphthol (22) was  $22.3 \pm 1.0\%$  from compound (19) which contained 93% of deuterium. This corresponds to formation of *ca.* 24% of (22a) from isotopically pure (19), in remarkably close agreement with the value of  $x$  obtained with the 1,4-oxide (15). Again, if we assume the same isotope effect  $k_H/k_D = 4.0$  for the

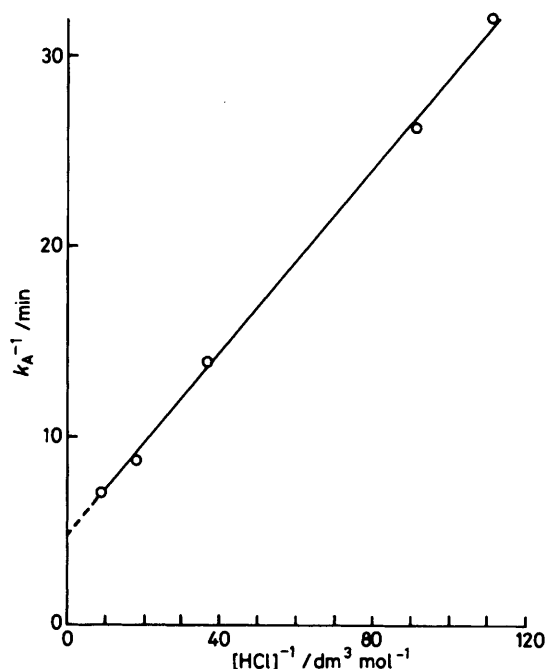
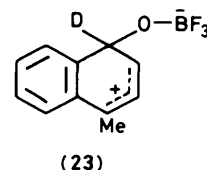


Figure 2. Double reciprocal plot to correlate the rate constant for aromatisation of the 1,4-oxide (19) with acid concentration

aromatisation of the intermediate (21), then the hydride shift *via* (21) is implicated for *ca.* 30% of the overall reaction (19)  $\rightarrow$  (22).

Although the 1,2-oxide (11) rearranges under neutral conditions only *via* the intermediate (17), the retention of deuterium is lower in the acid-catalysed rearrangement of [1- $^2H$ ](11),<sup>5</sup> because of a contribution from the pathway involving direct loss of deuterium from the 1-position (*cf.* step E in Scheme 2). The naphthalene 1,4-oxides do not rearrange at all without acid catalysis, but their acid-catalysed rearrangement is qualitatively similar to that occurring with the 1,2-oxide (11).<sup>5,15</sup> However, when the aromatisation of the 1,4-oxide (19) was catalysed by boron trifluoride under aprotic conditions, the observed retention of deuterium in the product (22) was 67%. This corresponds to *ca.* 90% of the overall reaction proceeding *via* the hydride shift (assuming the same isotope effect as before), due to the absence of a suitable base for direct removal of the deuterium from the 1-position of the intermediate (23).



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