Pyridinium Salts and Dihydropyridines; Mechanistic Studies of the Redox Reaction between Pyridinium Salts and Alkoxides in Tetrahydrofuran

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A model system for NAD-dependent redox reactions has been designed in an attempt to assess the involvement of covalent adducts as intermediates. The system consists of 3-substituted 1-n-heptylpyridinium salts and substituted benzyl alkoxides. Although covalent adducts were found in the reaction mixture, studies of substituent effects and other structural variations did not show that a covalent intermediate is on the reaction path.

BOTH the redox reactions of nicotinamide-dependent dehydrogenases with carbonyl compounds and alcohols and the redox reactions of analogous non-enzymic systems are understood to proceed essentially *via* hydride transfer between the reactants.[1] Evidence for this has accrued chiefly from the studies of isotope and substituent effects in the reactions of aromatic aldehydes and ketones.[2-5] Much attention has been paid recently to the possibility that such reactions might not occur by a direct, one-step hydride transfer, but that an intermediate may be involved.[2,6-8] In addition to synchronous hydride and proton transfer[1,2,4] many mechanistic schemes have been discussed ranging from a variety of π- and charge-transfer interactions[2,7-9] to fully covalent adducts of pyridine coenzyme and substrate.[10-12] The chemical background for nicotinamide coenzymes has also been greatly extended by the discovery that dihydropyridines are capable of reducing a wide range of substrates other than aldehydes and ketones.[13-20] With suitable substrates, radical pathways have been established.[21,22] In view of the plethora of often conflicting information, we felt that it would be valuable to examine a versatile model system which would enable the detailed interactions that take place between the reactants in pyridinium salt–dihydropyridine redox reactions to be studied.

RESULTS AND DISCUSSION

We have studied the reactions of the *N*-alkylpyridinium salts (1a—c) with the anions of substituted benzyl alcohols (2a—e) in tetrahydrofuran. These non-polar reaction conditions would be expected to maximise any intermediate-forming interactions between reactants. The conditions also provide a crude approximation to the generally non-polar active site of liver alcohol dehydrogenase.[23] The n-heptyl and morpholide side-chains were chosen to aid solubility; the tertiary amide also prevents the formation of amide anions which are known to give rise to complex polymeric products in reactions of nicotinamidium salts with strong bases.[24]

[1] H. Sund in 'Biological Oxidations,' ed. T. P. Singer, Interscience, New York, 1968, p. 603.
[2] J. P. Klinman, (*a*) *J. Biol. Chem.*, 1972, **247**, 7977; (*b*) *Biochemistry*, 1976, **15**, 2018.
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[13] C. Wang, S. Linnell, R. Rosenblum, and N. Wang, *Experientia*, 1971, **27**, 243.
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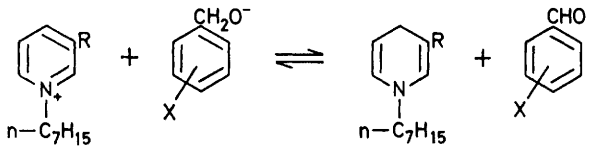
[19] K. Wallenfels, W. Ertel, and K. Friedrich, *Annalen*, 1973, 1663.
[20] U. K. Pandit, J. B. Steevens, and F. R. Mas Cabré, *Bioorg. Chem.*, 1973, **2**, 293; W. Tagaki, H. Sakai, Y. Yano, K. Ozeki, and Y. Shimuzu, *Tetrahedron Letters*, 1976, 2541.
[21] D. A. Widdowson, results presented at the Chemical Society Congress, Glasgow, 1976.
[22] A. Lombardo and D. C. Dittmer, *Bioorg. Chem.*, 1971, **1**, 400.
[23] H. Eklund, Bo Nordström, E. Zeppezauer, G. Söderlund, I. Ohlsson, T. Boiwe, and C.-I. Branden, *F.E.B.S. Letters*, 1974, **44**, 200.
[24] W.-H. Gündel, *Z. Naturforsch.*, 1974, **29b**, 556.

Operation of the Model System.—Solutions of the *N*-alkylpyridinium iodides or perchlorates (1a—c) with the lithium alkoxides (2a—e) afford aldehydes at room temperature under nitrogen (Scheme 1).[25] Oxidation only took place with the alkoxides; no oxidation was



(1) (2) (3) (4)

R for (1) and (3)
a; H
b; CO·N(CH$_2$·CH$_2$)$_2$O
c; SO$_2$·N(CH$_2$·CH$_2$)$_2$O

X for (2) and (4)
a; *p*—NMe$_2$
b; *p*—OMe
c; *p*—Me
d; H
e; *m*—Cl

SCHEME 1

detected when the corresponding alcohols were incubated under otherwise identical conditions. Only one previous example of the oxidation of an alcohol by a pyridinium salt has been reported.[26] The conversions into aldehyde that we obtained are shown in Table 1. With sulphonamide (1c) and the alkoxide (2a) it was possible to show by ^{1}H n.m.r. spectroscopy that no elimination or substitution side reactions took place. The same proportions of products were observed when the reaction was initiated with the dihydropyridine (3c) and the aldehyde (4a).

TABLE 1

Aldehyde produced (%) in reactions of pyridinium salts with lithium alkoxides in tetrahydrofuran at 20 °C

	Pyridinium salt		
Lithium alkoxide	(1a)	(1b)	(1c)
(2a)			63.3 ± 1.9
(2b)	0.56 ± 0.28	2.0 ± 1.2	20.0 ± 3.7
(2c)		1.3 ± 0.3	12.0 ± 0.3
(2d)	0.28 ± 0.14	0.61 ± 0.18	4.3 ± 1.2
(2e)	0.52 ± 0.04	0.70 ± 0.11	2.1 ± 0.2

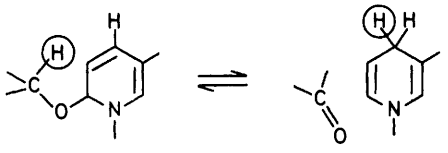
TABLE 2

Deuterium distribution in reactions of sulphonamides (1c) and (3c) with *p*-dimethylaminobenzaldehyde and *p*-dimethylaminophenylmethoxide (normalised peak intensities)

Reactants	(1c), (2a) (H)	(1c), (2a) (D)	(3c), (4a) (H)	(3c), (4a) (D)
(4a) CHO peak intensity	1.15	0.60	1.24	1.04
(1c) 4-H$_2$ peak intensity	1.00	1.00	1.00	1.00

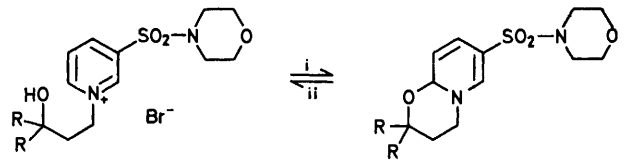
That this reaction is a hydrogen-transfer process analogous to the enzyme-mediated reaction was demonstrated by using [*methylene*-^{2}H]-(2a) and [4-^{2}H$_1$]-(3c) with the pyridinium salt (1c) and the aldehyde (4a), respectively. Deuterium was exchanged between the methylene group of the alkoxide and the 4-position of the dihydropyridine, as shown by ^{1}H n.m.r. spectroscopy, and the observed deuterium distribution confirmed that equilibrium had been attained (Table 2) in this case.

The Presence of Potential Intermediates in the Reaction Mixture.—It is to be expected that mixtures of pyridinium and alkoxide ions would contain an addition product analogous to the intermediate proposed by Hamilton [12] for NAD-mediated alcohol dehydrogenation (Scheme 2). Hamilton envisaged that the adduct (5) of an alcohol and



(5)

a pyridinium salt would undergo a thermally allowed electrocyclic hydrogen shift to afford the aldehyde and dihydropyridine. Analogies exist for such a rearrangement.[27,28]



(6) (7)

a; R = H, b; R = D

SCHEME 2 Reagents: i, KOBu^t; ii, HBr

In order to characterise the chemical and spectroscopic properties of such an adduct in the sulphonamide series, we prepared the bicyclic intramolecular adduct (7a) from the corresponding *N*-(3-hydroxypropyl)-pyridinium salt (6) by treatment of the latter with potassium t-butoxide in anhydrous acetonitrile. Addition occurred exclusively at the 6-position, and the u.v. spectrum of the cyclic adduct permitted it to be readily distinguished from the 1,4-dihydropyridine (3c) and the pyridinium salt (1c). Similarly, the addition of a solution of an alkoxide to a solution of the pyridinium perchlorate (1c) caused rapid formation of a 6-adduct, as shown by u.v. spectroscopy and by the isolation and partial characterisation of the adduct of allyl alkoxide.

The cyclic adduct (7a) was stable in solution with respect to the anion and the pyridinium salt, whereas the acyclic adducts gradually released anion to give an equilibrium mixture of adduct and ions. Both adduct types were rapidly converted into alcohol and pyridinium salt by acid, and both were slowly oxidised in solution in air, again to pyridinium salts.

If covalent adducts such as these are analogues of intermediates in NAD-mediated alcohol dehydrogenation, they should rearrange to the corresponding 1,4-dihydro-

[25] A. Shirra and C. J. Suckling, *Tetrahedron Letters*, 1975, 3323.
[26] K. Wallenfels and W. Hanstein, *Angew. Chem. Internat. Edn.*, 1965, **4**, 869.
[27] R. E. Manning and F. M. Schaefer, *Tetrahedron Letters*, 1974, 3343.
[28] K. Wallenfels and H. Schüly, *Annalen*, 1959, **621**, 178.

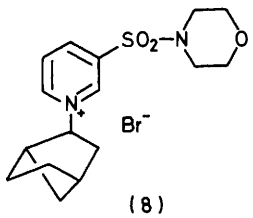
pyridine and aldehyde. Molecular models suggested that the postulated rearrangement of (7a) was feasible. However the cyclic adduct (7a) could not be induced to rearrange either at room temperature in solution or on heating to temperatures of up to 100 °C in the presence of carbonyl trapping reagents. This result is less surprising in view of the low yields in oxidation of alkoxides without electron-donating groups in the benzene ring. Nevertheless, we felt that it might be possible to demonstrate hydrogen transfer in the cyclic case by preparing the doubly deuteriated analogue (7b). After heating this compound at 100 °C for several days, no deuterium transfer to C-4 of the pyridine ring was observed. These results emphasise the possibility that fully covalent adducts of the Hamilton type do not lie along the reaction path for oxidation of alcohols in the model or the enzyme-catalysed reaction. Indeed covalent intermediates in general seem improbable in view of the evidence [20] against an alternative covalent adduct formed at C-4.[11] However, because an electron-releasing group in the alkoxide in our system is required for substantial oxidation to occur, it was necessary to examine the mechanism further by kinetic means.

Kinetic Studies.—Although it is in principle possible to study the redox reaction in either direction with our model system, unfortunately the formation of adduct was too rapid for study without rapid reaction techniques.

We therefore attempted to test the potential intermediacy of the ' Hamilton ' adduct by blocking adduct formation by steric hindrance. In the first attempt we used the bulky 2-norbornyl group (8) in place of the n-heptyl group on the pyridine nitrogen atom. However this compound was too unstable to be obtained analytically pure, and on treatment with base underwent elimination in competition with addition. We were unable to prepare a hindered pyridinium salt lacking a hydrogen atom β to the pyridine ring. We then thought that if a hindered alkoxide was used it might be possible to observe the redox behaviour in the absence of addition. Surprisingly, however, even t-butoxide added slowly to the n-heptylpyridinium sulphonamide, and the activated but hindered alkoxide (9) added as rapidly as the primary alkoxides. In the third approach, the 6-position of the pyridine ring was blocked by substitution with a phenyl group [compound (10)]. This compound was obtained by addition of phenylmagnesium bromide to the 6-unsubstituted pyridinium perchlorate [29] followed by oxidation with chloranil. On treatment of the 6-phenylpyridinium salt with phenylmethoxide in tetrahydrofuran, no u.v. maximum in the 303—312 nm region, characteristic of 6-addition, was observed; instead, a maximum at 355 nm appeared and was gradually shifted to 390 nm. Presumably this behaviour was due to initial addition to the 2-position with subsequent isomerisation to yield a 1,4-dihydro-adduct. Similar behaviour has been observed in the case of cyanide adding to 3,5-disubstituted pyridinium derivatives.[26,30]

[29] L. M. Thiessen, J. A. Lepoivre, and F. C. Alderweirelt, *Tetrahedron Letters*, 1974, 59.

Another potential solution to the problem, the preparation of activated derivatives of the cyclic adduct (7), suffers from the drawback that dissociation into ions could be envisaged as occurring immediately before hydrogen transfer and that hydrogen transfer might



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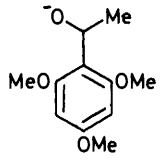

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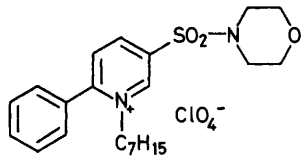


(10)

then take place within an intimate ion pair. Consequently, the only remaining approach appeared to be to gather circumstantial evidence from substituent effects, salt effects, kinetic isotope effects, and temperature effects upon the reaction rate. The reduction of the aldehydes (4b—e) by dihydropyridine (3c) was followed spectrophotometrically at 350 nm, a wavelength at which overlap between the dihydropyridine and adduct bands is small. At low concentrations (appropriate for spectroscopic study) the reaction is first-order in dihydropyridine and aldehyde for several hours, and rate constants were obtained from the inital rates. The values obtained correlated with the Hammett σ constant (σ^+ for *p*-MeO). Significant was the very small value of the

TABLE 3

Reduction of aldehydes by the dihydropyridine (3c) at 20 ± 0.1 °C

Aldehyde	Initial concentrations (mM) of aldehyde and dihydropyridine	No. of determinations	k / l mol^{-1} min^{-1}
(4b)	0.25	7	1.9 ± 0.2
	5.00 [a]	2	1.3 ± 0.4
(4c)	0.25	6	2.7 ± 0.2
(4d)	0.25	7	3.3 ± 0.3
(4e)	0.25	12	3.9 ± 0.2
Reduction by the deuteriodihydropyridine (3c)			
(4b)	0.25	3	0.74 ± 0.1
(4c)	0.25	3	0.95 ± 0.1
(4d)	0.25	3	1.0 ± 0.1
(4e)	0.25	3	1.2 ± 0.1

[a] By oxime analysis, reaction solution contained 5mM-$LiClO_4$. All other reactions were followed by u.v spectroscopy and the solutions contained in addition 0.25mM-$LiClO_4$.

reaction constant, 0.23, which indicates a very low degree of charge development in the transition state. Many studies of such substituent effects have been made for enzyme-catalysed reactions,[2-4] and the origin of our low value required investigation.

[30] R. E. Lyle and G. J. Gauthier, *Tetrahedron Letters*, 1965, 4615.

First, it is possible that hydrogen transfer does not occur in the rate-determining step. However, when the [4-^{2}H]dihydropyridine (3c) was used as a reductant, a kinetic isotope effect of 6—7 was found. This showed that hydrogen transfer was rate-limiting, as is usual in such reactions [2,4-7,31] The low value of ρ could also be taken as indicative of a radical reaction. However, in common with other reductions of carbonyl derivatives by dihydropyridines,[4,6] the presence of oxygen or radical-chain inhibitors (quinol or *p*-dinitrobenzene) did not quench the reductions. A side reaction of the dihydropyridine with *p*-dinitrobenzene in the absence of aldehyde was also observed.[21] A third explanation for the low ρ value could be that the lithium cation polarised the carbonyl group of the aldehyde before the rate-determining step.[6,14,18,32] This seemed unlikely in our case in view of the finding that the rate of reduction of *m*-chlorobenzaldehyde was not noticeably altered by changes in the lithium perchlorate concentration from zero to nearly four-fold excess over the aldehyde (Table 4).

TABLE 4

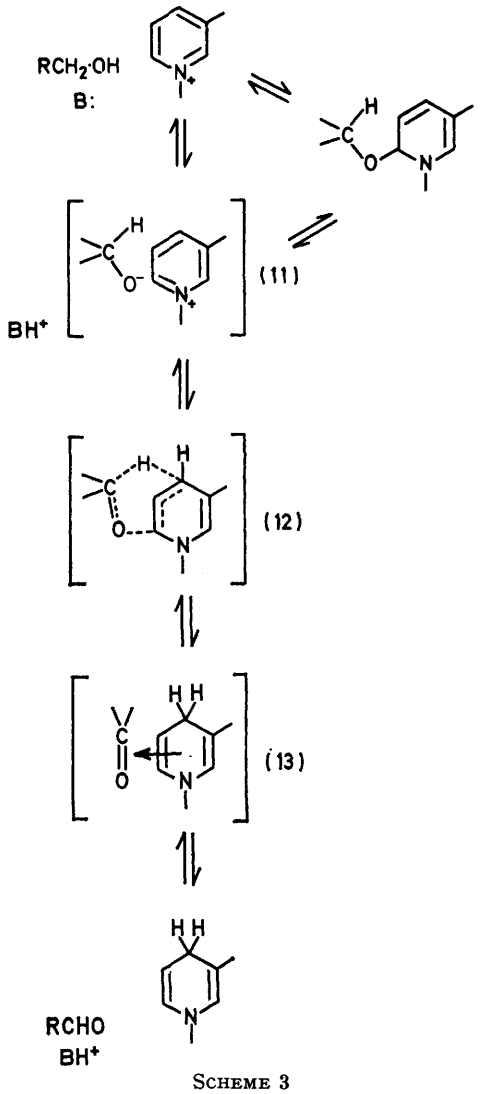
Reduction of *m*-chlorobenzaldehyde by the dihydropyridine (3c)

Concentrations (mM) (3c)	(4c)	[$LiClO_4$]/ mM	No. of determinations	Temp. (°C) (±0.1)	k / l mol^{-1} min^{-1}
0.25	0.25	0.25	12	20.0	3.9 ± 0.2
0.42	0.66	0.66	1	29.0	5.7
0.42	1.33	1.33	2	29.0	5.7
0.17	1.33	1.33	2	29.0	7.2
0.17	1.33	1.33	3	35.5	11.1 ± 0.7
0.17	1.33		2	35.5	11.1
0.25	0.25	0.25	2	37.0	14 [a]
0.25	0.25	0.25	2	37.0	14 [b]
0.33	0.33	0.33	2	37.0	14 ± 3
0.57	0.83	0.83	3	47.0	31 ± 3
0.57	1.66	1.66	2	47.0	29
0.57	2.26	2.26	2	47.0	27
0.57	0.33	0.33	2	47.0	29
0.57	0.83		2	47.0	32
0.57	0.83	1.66	1	47.0	33
0.57	0.83	3.22	2	47.0	32
0.08	1.00	1.00	3	47.0	29
0.23	1.00	1.00	3	47.0	34
0.46	1.00	1.00	3	47.0	34

[a] Contained in addition 0.025mM-quinol. [b] Contained in addition 0.25mM-quinol.

A low ρ value could also be explained if the cyclic mechanism of Scheme 2 were followed, provided that bond formation between the appearing alkoxide and the pyridine ring was well advanced in the transition state. Such a mechanism is also consistent with the entropy of activation for the reaction, −74 J K^{-1} mol^{-1}, a large value for a bimolecular reaction and similar to entropies for electrocyclic reactions.[33] A value of similar magnitude has been found for the reduction of 2,2,2-trifluoroacetophenone in aqueous solution by n-propyldihydronicotinamide.[34]

From these results it is not possible to rule out the 'Hamilton' intermediate as kinetically impossible in this model system or as having the wrong intrinsic chemical reactivity to be an intermediate in the model or enzyme-catalysed reactions. It has already been suggested from model studies [22] that the oxygen of the carbonyl group of the aldehyde or ketone substrate should be close to C-2 or -6 of the dihydropyridine ring and the



SCHEME 3

C=O bond in a plane parallel to the dihydropyridine ring: a similar substrate–coenzyme orientation was deduced by Prelog [35] for liver alcohol dehydrogenase-catalysed reduction of cycloalkanones. Our low ρ value can be accommodated by assuming a similar interaction between the dihydropyridine (3c) and its substrates (Scheme 3). The transition state can then be envisaged as a six-centred electrocyclic array in which only slight polaris-

[31] C. H. Suelter and D. E. Metzler, *Biochim. Biophys. Acta*, 1960, **44**, 23.
[32] R. N. Lewis and J. R. Wright, *J. Amer. Chem. Soc.*, 1952, **74**, 1257.
[33] P. Beltrame in 'Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. Tipper, Elsevier, Amsterdam, 1972, vol. 9, p. 108; W. E. Richardson and H. E. O'Neal, *ibid.*, vol. 5, p. 381.
[34] P. van Eikeren and D. L. Grier, *J. Amer. Chem. Soc.*, 1976, **98**, 5655.
[35] V. Prelog, *Pure Appl. Chem.*, 1964, **9**, 119.

ation of the carbonyl group remains (12). After rate-determining hydrogen transfer an ion pair (11) is reached which then produces the equilibrium mixture of ' Hamilton ' adduct and free ions. Since it has been shown that proton transfer from alcohol in the liver alcohol dehydrogenase catalysed reaction precedes the redox step,[36] it may be that a similar sequence of events takes place at the enzyme's active site. In this case, rapid protonation of the reduced oxygen by the acidic group on the enzyme surface would avoid the need to form a fully covalent adduct.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded at 100 MHz with a Perkin-Elmer R14 spectrometer. U.v. spectra ($\lambda_{max.}$ in nm; ε in parentheses) were measured with a Pye-Unicam SP 800 or 8000 spectrophotometer, equipped, for kinetic studies, with a scale expansion unit and an external recorder. I.r. spectra ($\nu_{max.}$ in cm^{-1}) were recorded with a Perkin-Elmer 257 spectrometer.

Synthetic Studies.—Pyridine-3-carbomorpholide. Nicotinohydrazide (4.11 g) dissolved in 2M-hydrochloric acid (15 ml) was cooled to 0 °C. An ice-cold solution of sodium nitrite (2.07 g) in water (15 ml) was added dropwise with stirring: this caused the azide to precipitate. The reaction was allowed to continue at 0 °C for 1 h and the azide was extracted into chloroform (60 ml) containing triethylamine (3.03 g). Morpholine (2.61 g) was added to the extract and the solution left overnight at room temperature. The solution was extracted with 2M-sodium carbonate (50 ml) and the organic layer dried (Na_2SO_4) and evaporated to yield the required *pyridine* as a pale yellow oil which slowly crystallised (3.9 g, 66%); m.p. 60—63° (from ethyl acetate) (Found: C, 61.9; H, 6.4; N, 14.6. $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.3; N, 14.6%), τ($CDCl_3$) 1.30br (s, H-2 and -4), 2.25 (d, H-6), 2.62 (m, H-5), and 6.42br [$(CH_2{\cdot}CH_2)_2N$], $\lambda_{max.}$ (95% EtOH) 204 (8 020), 256 (3 960), 264 (3 860), and 269sh (2 970).

Pyridine-3-sulphonomorpholide. Pyridine-3-sulphonic acid (15.9 g) intimately mixed with phosphorus pentachloride (22.9 g) was heated until the phosphoryl chloride produced had boiled for 1 h. The solution was allowed to cool to room temperature. A solution of morpholine (28 g) in toluene (75 ml) was added cautiously with swirling followed by more toluene (100 ml). The volatile compounds were removed *in vacuo*. Saturated aqueous sodium hydrogen carbonate (100 ml) was added to the residue and the organic product extracted into chloroform (3 × 50 ml). Drying (Na_2SO_4) and evaporation *in vacuo* left an oil which readily crystallised. The required *pyridine* (21 g, 92%) was recrystallised from ethanol; m.p. 119—121° (Found: C, 47.4; H, 5.4; N, 12.2; S, 14.1. $C_9H_{12}N_2O_3S$ requires C, 47.4; H, 5.3; N, 12.3; S, 14.1%), τ($CDCl_3$) 1.30 (m, H-2 and -4), 2.13 (d, H-6), 2.70 (H-5), 6.35 (OCH_2), and 7.05 (NCH_2), $\lambda_{max.}$ (95% EtOH) 203 (7 340), 255 (3 100), 260 (3 180), and 264sh (2 670).

Pyridinium salts. Pyridinium halides were obtained by heating the pyridine and alkyl halide under reflux in butan-1-ol or toluene for 18—48 h. Pyridinium perchlorates were prepared by metathesis of the corresponding halide with an equimolar quantity of silver perchlorate in methanolic solution. The precipitated silver halide was filtered off, the solution was concentrated, and crystallisation was induced by adding ether and chilling.

1-*Heptylpyridinium iodide* (1a), prepared in toluene in 100% yield and recrystallised from acetone at −20 °C, is very hygroscopic; m.p. 52—53° (Found: C, 46.9; H, 6.5; N, 4.4. $C_{12}H_{20}IN$ requires C, 47.2; H, 6.6; N, 4.6%), τ($CDCl_3$) 0.72 (d, $J_{2.3}$ 6.3 Hz, H-2 and -6), 1.51 (t, H-4), 1.98 (t, $J_{4.5}$ 7.1 Hz, H-3 and -5), 5.18 (t, N^+CH_2), and 7.99br (2 H), 8.73br (8 H), and 9.20br (3 H, t) ($[CH_2]_5CH_3$), $\lambda_{max.}$ (95% EtOH) 228 (6 100), 260 (6 770), and 265sh (6 200).

1-*Heptyl-3-morpholinocarbonylpyridinium iodide* (1b), prepared in butan-1-ol in 81% yield and recrystallised from tetrahydrofuran at −20 °C, had m.p. 120—122° (Found: C, 48.8; H, 6.4; N, 6.5. $C_{17}H_{27}IN_2O_2$ requires C, 48.8; H, 6.5; N, 6.7%), τ($CDCl_3$) 0.85 (m, H-2 and -6), 1.69 (d, $J_{4.5}$ 7.1 Hz, H-4), 1.88 (t, H-5), 5.19 (t, N^+CH_2), 6.3br [$N(CH_2CH_2)_2O$], and 7.98br (2 H), 8.73br (8 H), and 9.17br (3 H, t) ($[CH_2]_5CH_3$), $\lambda_{max.}$ (95% EtOH) 218 (14 000) and 268 (5 640).

1-*Heptyl-3-morpholinosulphonylpyridinium iodide* (1c), prepared in butan-1-ol in 67% yield and recrystallised from hot water, gave pale yellow needles, m.p. 146—148° (Found: C, 42.4; H, 6.1; N, 6.0; S, 7.1. $C_{16}H_{27}IN_2O_3S$ requires C, 42.3; H, 6.0; N, 6.2; S, 7.1%), τ [$(CD_3)_2SO$] 0.70 (s, H-2), 0.84 (d, $J_{5.6}$ 8.3 Hz, H-6), 1.27 (d, H-4), 1.62 (t, $J_{4.5}$ 5.7 Hz, H-5), 5.35 (t, N^+CH_2), 6.39 (m, OCH_2), 6.90 (m, NCH_2), and 8.08 (2 H, m), 8.75 (8 H, m), and 9.09 (3 H, t) ($[CH_2]_5CH_3$), $\lambda_{max.}$ (95% EtOH) 219 (19 200) and 268 (40 000), $\nu_{max.}$ (KCl) 1 620 and 1 580. The corresponding *perchlorate* crystallised from methanol as needles, m.p. 134—135° (Found: C, 44.1; H, 6.2; N, 6.3; S, 7.6. $C_{16}H_{27}ClNO_7S$ requires C, 44.2; H, 6.2; N, 6.5; S, 7.6%).

1-(3-*Hydroxypropyl*)-3-(*morpholinosulphonyl*)*pyridinium bromide* (6), prepared in butan-1-ol in 90% yield, was a glass which could not be induced to crystallise, τ [$(CD_3)_2SO$] 0.50 (m, H-2 and -6), 1.02br (d, H-4), 1.64 (m, H-5), 5.22 and 5.57 (CH_2OH and N^+CH_2), 6.34 (m, OCH_2), 6.86 (m, NCH_2), and 7.86br (t, CH_2).

1-(2-*Norbornyl*)-3-*morpholinosulphonylpyridinium bromide* (8), prepared in 20% yield in butan-1-ol and recrystallised from methanol–ether, gave needles, m.p. 123—124° (the principal product of this reaction was the hydrobromide of pyridine-3-sulphonomorpholide), τ [$(CD_3)_2SO$] 0.45 (s, H-2), 0.49 (d, H-6), 1.21 (d, H-4), 1.76 (t, H-5), 5.17 (t, N^+CH), 6.46 (m, OCH_2), 6.76 (m, NCH_2), and 8.04 (3 H, m), 8.62 (3 H, m), and 9.06 (4 H, t, aliphatic).

1-*Heptyl-1,4-dihydro-3-morpholinosulphonylpyridine* (3c). 1-Heptyl-3-morpholinosulphonylpyridinium iodide (1 g) was dissolved in water (100 ml) at room temperature and sodium carbonate (5 g) and sodium dithionite (5 g) in water (25 ml) were added dropwise with stirring over 2 h. The solution became turbid and was left in the refrigerator overnight. The precipitated product was filtered off and recrystallised at −20 °C from methanol containing a few drops of water. The *dihydropyridine* was obtained as pale yellow needles, m.p. 65—66° (600 mg, 75%), unstable in strong light (Found: C, 58.4; H, 8.7; N, 8.6; S, 10.0. $C_{16}H_{28}N_2O_3S$ requires C, 58.5; H, 8.6; N, 8.5; S, 9.8%), τ [$(CD_3)SO$] 3.35 (s, H-2), 4.20 (d, J 8.5 Hz, H-6), 5.26 (m, H-5), 6.47 (m, OCH_2), 7.05 (m, NCH_2), 6.9 (H-4), 8.5—8.9 (m, $[CH_2]_6$), and 9.17br (s, CH_3), $\lambda_{max.}$ (tetrahydrofuran) 226 (2 675) and 323 (2 910), $\nu_{max.}$ (Nujol) 1 670 and 1 590. An analogous preparation with deuterium oxide as solvent afforded the 4-deuteriodihydropyridine containing 0.8 atoms of deuterium per molecule as shown by ^{1}H n.m.r. spectroscopy.

[36] M. F. Dunn, *Structure and Bonding*, 1975, **23**, 89.

3,4-Dihydro-7-morpholinosulphonyl-2H-pyrido[2,1-b][1,3]-*oxazine* (7). 1-(3-Hydroxypropyl-3-morpholinosulphonyl-pyridinium iodide (590 mg) was dissolved in anhydrous acetonitrile (10 ml) and potassium t-butoxide (160 mg) added. The solution was stirred for 4 h and set aside overnight. Brine (100 ml) and dichloromethane (100 ml) were added, the mixture was shaken, and the organic phase was separated. Drying (Mg_2SO_4) and evaporation to dryness left a gum which crystallised on trituration with light petroleum. Recrystallised from acetonitrile–petroleum (b.p. 60—80 °C), the *product* had m.p. 151—153° and was obtained pure in 47% yield (Found: C, 50.7; H, 6.4; N, 9.5. $C_{12}H_{18}N_2O_4S$ requires C, 50.3; H, 6.3; N, 9.8%), τ [$(CD_3)_2$-SO] 2.85 (s, H-2), 3.80 (d, $J_{4,5}$ 11 Hz, H-4), 4.44 (d, $J_{5,6}$ 4 Hz, H-6), 4.95 (dd, H-5), 6.10 (m, OCH_2), 6.47 (m), and 6.54 (m) [$O(CH_2{\cdot}CH_2)_2N$], and 8.37 (t, CH_2), $\lambda_{max.}$ (tetrahydrofuran) 230 (10 000) and 312 (7 810), $\nu_{max.}$ (film) 1 635 and 1 575.

1-Heptyl-3-morpholinosulphonyl-6-phenylpyridinium perchlorate (10). To a suspension of magnesium turnings (250 mg) in dry tetrahydrofuran (25 ml) was added bromobenzene (1.57 g) in small portions over 30 min at room temperature. Formation of the Grignard reagent was complete in 1 h. The solution was then gently brought to the boil and pyridinium perchlorate (1c) (3.7 g) was added; the pyridinium salt dissolved rapidly. After 2 h, a solution of chloranil (2.46 g) in tetrahydrofuran (50 ml) was added dropwise, to give a purple solution. After cooling the solution to 0 °C, gaseous hydrogen bromide was bubbled through until a pale yellow colouration was observed. The solution was evaporated to dryness and the residue partitioned between water (100 ml) and toluene (100 ml). The toluene layer contained tetrachlorohydroquinone and the water layer the required pyridinium salt. The aqueous solution was evaporated to dryness and the colourless residue (bromide salts) dissolved in methanol (25 ml). The bromides were converted into the corresponding perchlorates by addition of silver perchlorate (4.2 g) in methanol (50 ml). Silver bromide was filtered off and the solution evaporated to leave a gum which was chromatographed on silica (50 g) (elution with 20% acetone in dichloromethane). Evaporation of the eluates afforded the *pyridinium perchlorate* (600 mg) as a solid which crystallised as plates (from methanol), m.p. 218—219° (Found: C, 52.6; H, 6.4; N, 5.5. $C_{22}H_{31}ClN_2O_7S$ requires C, 52.5; H, 6.2; N, 5.6%), τ [$(CD_3)_2SO$] 0.50 (s, H-2), 1.30 (d, H-4), 1.89 (d, H-5), 2.45 (s, Ph), 5.51 (t, N^+CH_2), 6.36 (t, OCH_2), 6.89 (m, NCH_2), and 8.41 (2 H, m), 8.95 (8 H, m), and 9.20br (3 H, t)([CH_2]$_5CH_3$).

Adduct of allyl alcohol and the pyridinium salt (1c). Powdered lithium hydride (200 mg) was added to dry allyl alcohol (10 ml). When effervescence had ceased, dry tetrahydrofuran (10 ml) was added and the solution cooled to 0 °C. Powdered pyridinium bromide (1c) (500 mg) was added and a homogeneous solution was rapidly obtained. After 3 h at 4 °C, the solution was mixed with ice–water (50 ml) and chloroform (25 ml). The chloroform layer was separated and the aqueous phase extracted with more chloroform (25 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The product, an oil, had $\lambda_{max.}$ 305 nm in tetrahydrofuran and its i.r. and ^{1}H n.m.r. spectra were very similar to those of the cyclic adduct (7a). A solution of the product became gradually alkaline. The n.m.r. spectrum (60 MHz) showed τ($CDCl_3$) 2.72 (s, H-2), 3.40 (dd, H-4), 3.7—4.4 and 4.6—5.1 (allyl CH), 4.39 (d, H-6), 4.71 (dd, H-5), 5.90 (m, OCH_2), 6.28 (m), and 6.5—7.1 [$O(CH_2{\cdot}CH_2)N$], 8.1—8.9 ([CH_2]$_5$), and 9.05 (t, CH_3).

Attempts to rearrange the adducts (7a *and* b). (1) The adduct (7a) (100 mg) was heated under reflux in tetrahydrofuran (25 ml). After 3½ h, no change in the u.v. spectrum was observed.

(2) The adduct (7a) (110 mg) was dissolved in methanol and a solution of sodium borohydride (50 mg) in methanol (10 ml) containing a drop of aqueous sodium hydroxide (2M) was added over 20 min. After 18 h at room temperature, the organic products were extracted into chloroform. The product obtained on evaporation had an i.r. spectrum identical with that of starting material.

(3) Experiment (2) was repeated except that the solution was heated under reflux. An identical result was obtained.

(4) The adduct (7a) (100 mg) and the deuteriated adduct (7b) (100 mg) were separately dissolved in [$^2H_6$]dimethyl sulphoxide and sealed in n.m.r. tubes. The solutions were heated at 100 °C. The ^{1}H n.m.r. spectra were observed at intervals over 5 days, but no change in either peak positions or deuterium distribution was observed.

(5) The deuteriated adduct (7b) (290 mg) was dissolved in dry tetrahydrofuran (50 ml) and anhydrous lithium iodide (133 mg) was added. The solution was heated under reflux under nitrogen for 68 h. After evaporation, the organic product was extracted into chloroform and examined by ^{1}H n.m.r. spectroscopy. Again no deuterium transfer was observed.

Reactants and Solvent for Mechanistic Studies.—Liquid alcohols and aldehydes were redistilled and stored over molecular sieves. Lithium perchlorate was dried *in vacuo* over phosphorus pentaoxide. Tetrahydrofuran was freshly distilled from lithium aluminium hydride.

Equilibrium Studies.—Alkoxide solutions were prepared by treatment of the appropriate alcohol with ethereal methyl-lithium under nitrogen. They were made up to the required volume with dry tetrahydrofuran added from a syringe and their concentrations determined by titration of two samples. A solution of the appropriate pyridinium salt was then added and the resulting solution kept under nitrogen for 1—5 days. Concentrations of pyridinium salts used were: (1a and b) 5×10^{-4} and 8×10^{-4}M; (1c) 10^{-4} and 2×10^{-4}M. Alkoxides were used in equimolar quantities. Control experiments were carried out in the absence of pyridinium salts. For determination of small quantities of aldehydes, the reaction mixture was quenched with methanol and evaporated to dryness. The residue was dissolved in 2M-hydrochloric acid (30 ml) and ether (30 ml) and the mixture shaken vigorously. The aqueous layer was washed with two further portions of ether (each 25 ml) and the combined extracts washed with brine (2 × 25 ml). After drying over freshly dried sodium sulphate, the ether layer was evaporated to dryness and the residue assayed for aldehyde by the method of Roe and Mitchell.[37] Methanol was used as solvent. For determination of *p*-dimethylaminobenzaldehyde, the reaction mixture was evaporated to dryness and dissolved in toluene (10 ml) and water (10 ml). The process was repeated and the residue dissolved in [$^2H_6$]dimethyl sulphoxide and examined by ^{1}H n.m.r. spectroscopy. The results quoted in Table 1 are each derived from 3—7 independent determinations of both control and 'live' experiments. Reactions of dihydropyridine (3c) were initiated by adding a solution of the appropriate aldehyde to a solution of the dihydropyridine and lithium

[37] H. R. Roe and J. Mitchell, *Analyt. Chem.*, 1951, **23**, 1758.

iodide or perchlorate, all in tetrahydrofuran, under nitrogen. The work-up and assay were as described above.

Kinetic Studies.—Reactions followed by sampling were carried out as described for the equilibrium studies. The concentration was 5×10^{-4}M for each reactant. U.v. spectroscopic studies were carried out by using stoppered 1 cm cells; reactions were initiated by addition of the dihydropyridine or the alkoxide. The concentrations were as listed in Tables 3 and 4. Radical inhibitors (quinol and *p*-dinitrobenzene) were added at 10 and 100% of the dihydropyridine concentrations.

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