A Direct Method based on Hydride Exchange for Determining the Redox Potentials of 1,4-Dihydropyridines Related Structurally to Nicotine Adenine Dinucleotide (NADH)

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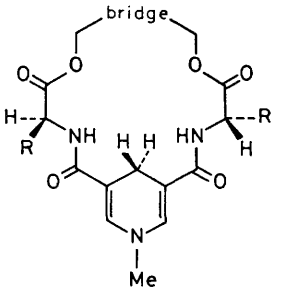
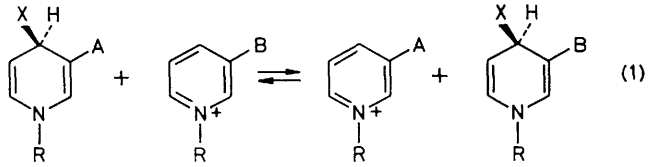
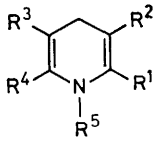
The relative two-electron redox potentials of *N*-substituted 1,4-dihydropyridines related to NADH can be determined by a direct method in which the equilibrium composition of a 1,4-dihydropyridine–pyridinium salt mixture is determined by ^{1}H n.m.r. spectroscopy.

An essential element in design of artificial hydrogenases like (**1**)[1,2] (NADH mimics) is knowledge of the (relative) two-electron redox potentials[3] of the 1,4-dihydropyridines. Such information is required in practice for nonaqueous (or on occasion, partially aqueous) solvents in which reductions are usually done. An indirect and relative method developed by



(1)



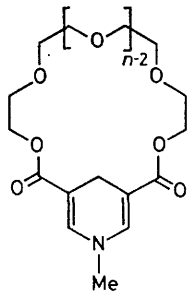


(2) $R^1 = R^3 = R^4 = H$; $R^2 = CONH_2$; $R^5 = PhCH_2$
(3) $R^1 = R^4 = Me$; $R^2 = R^3 = CO_2Et$; $R^5 = Me$
(4) $R^1 = R^4 = H$; $R^2 = R^3 = CONHEt$; $R^5 = Me$
(5) $R^1 = R^4 = H$; $R^2 = R^3 = CONEt_2$; $R^5 = Me$
(6) $R^1 = R^4 = H$; $R^2 = R^3 = COEt$; $R^5 = Me$
(7) $R^1 = R^4 = H$; $R^2 = R^3 = COEt$; $R^5 = Pr^i$
(8) $R^1 = R^4 = H$; $R^2 = R^3 = COEt$; $R^5 = PhCH_2$
(9) $R^1 = R^4 = H$; $R^2 = R^3 = CONH_2$; $R^5 = Me$
(11) $R^1 = R^4 = H$; $R^2 = R^3 = CONH_2$; R^5 = 2,6-dichlorobenzyl
(12) $R^1 = R^3 = R^4 = H$; $R^2 = CN$; R^5 = 2,6-dichlorobenzyl
(13) $R^1 = R^3 = R^4 = H$; $R^2 = CONH_2$; R^5 = ribosyl adenosyl diphosphate
(14) $R^1 = R^3 = R^4 = H$; $R^2 = COMe$; $R^5 = Me$
(15) $R^1 = R^3 = R^4 = H$; $R^2 = CONH_2$; $R^5 = Me$
(16) $R^1 = R^3 = R^4 = H$; $R^2 = COEt$; $R^5 = Me$
(17) $R^1 = R^3 = R^4 = H$; $R^2 = CONMe_2$; $R^5 = Pr^n$

Wallenfels and Dieckman[4] is often used to obtain the two-electron potentials. Two structurally different pyridinium salts are allowed to equilibrate in aqueous solution in the presence of cyanide ion as shown in equation (1) (X=CN). If the addition of cyanide to the pyridinium salts is reversible and occurs only at the 4-positions the equilibrium constant for equation (1) can be measured. The assumption is then made that this equilibrium constant is identical to that for direct 'hydride'† exchange (X=H in equation 1). The redox potential in aqueous solution of NADH *vs.* normal hydrogen electrode at 20 °C and pH 7 is −315 mV, which value is then used as a marker in calibrating relative redox potentials determined by the cyanide affinity method. This method, although useful, is based on an approximation and, moreover, is in practice not well suited for determinations in nonaqueous solvents.

We have measured *directly* in non- or partially-aqueous solvents using ^1H n.m.r. spectroscopy the values for the

† 'Hydride' is used here as a descriptor of the entity being transferred; no mechanistic implications are intended.



(10) a; $n = 3$
b; $n = 4$
c; $n = 5$

Table 1. Redox potentials of selected 1,4-dihydropyridines

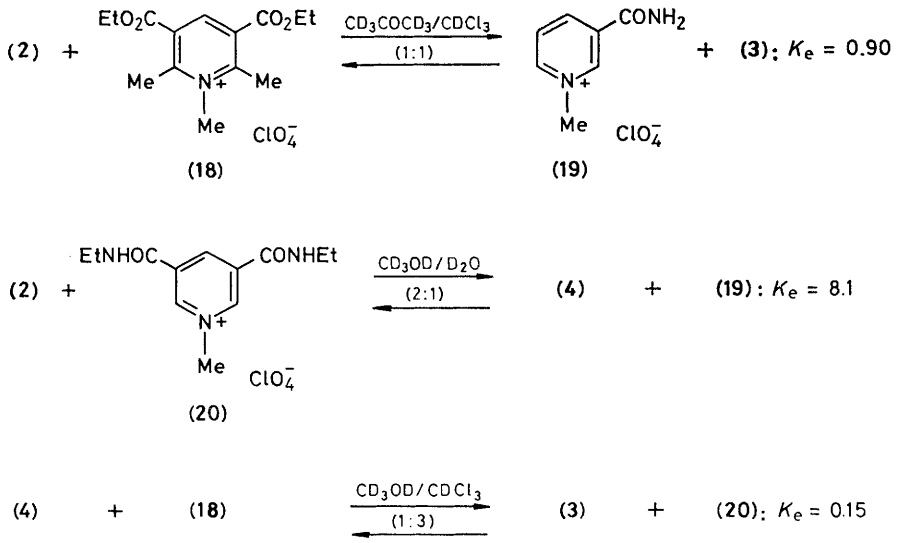
Compound	Method	Redox potential (20 °C) in mV
(11)	Cyanide affinity[a]	−249
(8)	Direct exchange	−258
(6)	,,	−260
(10a—c)	,,	−263
(7)	,,	−263
(12)	Cyanide affinity	−290
(9)	Direct exchange	−305
(13)	Cyanide affinity	−320
(4)	Direct exchange	−334
(14)	Cyanide affinity	−334
(2)	,,	−362
(3)	Direct exchange	−363
(5)	,,	−398
(15)	Cyanide affinity	−403
(16)	,,	−408
(17)	,,	−434

[a] Cyanide affinity values taken from ref. 4.

equilibrium of equation (1) for 'hydride' exchange. This exchange reaction[5,6] between the 4-positions of two different partners at 20 °C or lower is more rapid than transfer of 'hydride' to a 2- or 6-position of the pyridinium skeleton. By using a selected group of 1,4-dihydropyridine–pyridinium salt couples a relative scale of redox potentials was set up. To obtain experimentally measurable integrations the equilibrium constant for the measured reaction must correspond to $\Delta E <$ *ca.* 75 mV, *i.e.* roughly a 90:10 ratio of dihydropyridine–pyridinium salt at equilibrium.‡ Data for various 1,4-dihydropyridines are listed in Table 1 in order of increasing redox potential. The absolute redox potentials are relative to *N*-benzyl-1,4-dihydronicotinamide (**2**), which was *assumed* to have also in nonaqueous solution the redox potential of −361 mV.[4b]

The equilibria of Scheme 1, each equilibrium constant being approached from both sides, were determined in different solvents. From the equilibrium constant for the first two reactions one calculates $K_e = 0.11$ for the third reaction, in good agreement with experiment ($K_e = 0.15$). Similar cross checks were made for the other experimental points given in

‡ Freshly prepared 1,4-dihydropyridine (0.1 mmol) and pyridinium salt (0.1 mmol) were weighed or pipetted from stock solution into an n.m.r. tube containing 0.5 ml of solvent. Equilibrium from either side is generally achieved within 2 h. Relative concentrations were determined by peak integrations (continuous wave mode); an internal standard, 1,1,2,2-tetrachloroethane, was used in most cases. The signals were identified by comparison with known samples. The accuracy of the equilibrium constants approached from both sides is ± 10%.



Scheme 1

Table 1. No attempt has been made to use the cyanide affinity method for the compounds and solvents described here.

Structural changes that will improve the reducing power of 1,4-dihydropyridines are (a) introduction of carboxamide groups, this effect being enhanced by alkylation of the carboxamide, and (b) introduction of substituents at the 2,6-positions. Evaluations of the effect of bridging across the 3,5-positions in compounds (**1**)[1] will be reported in due course.

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