Complexation of NADH Analogues with β-Cyclodextrin: Inhibitory Effects of β-Cyclodextrin against Hydration and Copper(II) and Hexacyanoferrate(3−) Oxidation of 1,4-Dihydronicotinamides

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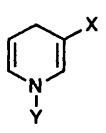
Fluorescent properties and reaction kinetics of the coenzyme NADH analogues 1(Y),3(X)-disubstituted-1,4-dihydropyridines (Y = benzyl or *para*-substituted phenyl; X = $CONH_2$, $CSNH_2$, CO_2Me, Ac) have been investigated in the presence of β-cyclodextrin (β-CD). From fluorescence measurements, it is concluded that the NADH analogues form 1:1 inclusion complexes with β-CD. The association constant varies sensitively with the nature of the substituents. The proton-catalysed hydration, copper(II) and hexacyanoferrate(3−) ion oxidation reactions of the NADH analogues are retarded by the presence of β-CD. The protective effects of β-CD against the reactions of NADH analogues are attributed to the inaccessibility of the reacting ions to the NADH analogue molecules included in the β-CD cavity, and destabilization of the reaction intermediates or transition states of the rate-determining steps.

Cyclodextrins (CDs) are cyclic oligosaccharides that possess hydrophobic binding cavities capable of forming inclusion complexes with a variety of organic molecules in aqueous solution. They have attracted widespread interest as a model for studies of enzyme–substrate interactions,[1] and have been used for selective synthetic strategies.[2]

1,4-Dihydronicotinamides (NAHs) are widely investigated as model compounds of NADH, a coenzyme for many dehydrogenases.[3] Several reports have appeared using cyclodextrins as media or frameworks for reactions of NADH or its model compounds.[4–10] It was shown that β-cyclodextrin (β-CD) accelerates the electrocatalytic oxidation of NADH by ferrocenecarboxylic acid,[4] whereas it retards the reduction of ninhydrin with 1-benzyl-1,4-dihydronicotinamide (BNAH)[5] and the hydration reaction of NAHs.[5,6] β-CD–1,4-dihydronicotinamides were prepared and utilized as models for NADH-dependent enzyme complexes in reductions of ninhydrin[6,7] and cytochrome *c* using redox dyes as electron mediators.[8] The compounds showed a higher rate in the reduction of the substrates[6–8] and a slower hydration rate[6] when compared with free NAHs. β-CD was also exploited as a medium to provide a chiral environment for asymmetric reduction of aryl trifluoromethyl ketones with achiral 1-propyl-1,4-dihydronicotinamide, though the magnitude of asymmetric bias is small.[9] The association constants of various NAHs with flavocyclodextrin, and rate constants for the redox reaction between them, were determined.[10] The large effects of β-CD on the reactions involving NADH model compounds were ascribed to the complexation of either substrate or NADH model compound with β-CD. The crystal structure of β-CD–nicotinamide (1:1) complex was reported.[11]

This paper presents results of fluorimetric studies on the inclusion of NADH analogues **1–4** into β-CD. The dependence of the association constant on the 1- and 3-substituent of the 1,4-dihydropyridine was obtained. Furthermore, effects of β-CD on the rates of hydration and copper(II) and hexacyanoferrate(3−) oxidation of NADH analogues are described, and correlated with the inclusion phenomena.



1; X = $CONH_2$, **a**; Y = $PhCH_2$, **b**; Y = *p*-MeC_6H_4, **c**; Y = *p*-$MeOC_6H_4$, **d**; Y = Ph, **e**; Y = *p*-ClC_6H_4, **f**; Y = *p*-NCC_6H_4

2; X = $CSNH_2$, Y = $PhCH_2$
3; X = CO_2Me, Y = $PhCH_2$
4; X = COMe, Y = $PhCH_2$

Experimental

Materials.—NADH analogues **1–4** were prepared by sodium dithionite reduction of the corresponding pyridinium salts as described in an earlier study.[12] β-CD was purchased from Aldrich and used as received. Concentration of β-CD was calculated from optical rotation data taken with a JASCO DIP-140 polarimeter at 25 °C using $[\alpha]_D^{25}$ 162.5°.[1a] Water was deionized and was then distilled in glass from acidic $KMnO_4$.

Preparation of Sample Solutions.—The solutions for spectral measurements and kinetic studies were prepared by addition of an ethanolic solution of NADH analogue to appropriate aqueous solutions of β-CD. Ionic strength of the final solutions was held constant at 0.1 mol dm^{-3} with NaCl, and the composition of solvent in the final mixtures was 5% (v/v) ethanol–95% water.

Fluorescence Measurements.—Fluorescence spectra of NADH analogues in the presence of various concentrations of β-CD were recorded on a Hitachi F-3010 spectrofluorimeter at 25 °C. The excitation wavelengths were their absorption maxima (≈350 nm). The solutions were adjusted to pH 9 with 0.01 mol dm^{-3} borate buffer to suppress the hydration reaction of NADH analogues (*vide infra*): under these conditions no appreciable change in absorbance or fluorescence intensity was observed for at least 3 h. To determine the association constant (K) of NADH analogues with β-CD from fluorescence data, fluorescence intensities of 1.0×10^{-5} mol dm^{-3} NADH analogues were measured in the presence of β-CD, the concentration of which was varied from 2.0×10^{-4} to 1.0×10^{-2} mol dm^{-3}. (Details of the calculation of the association constants are described in the Results section.)

Kinetics of the Reactions of NADH Analogues.—The hydration, copper(II) and hexacyanoferrate(3−) oxidation reactions of NADH analogues (XDHP) were initiated by addition of a solution of an XDHP *via* microsyringe to an appropriate β-CD solution in a thermostatted UV cell at 25 °C. The reactions were followed by a decrease in absorbance of

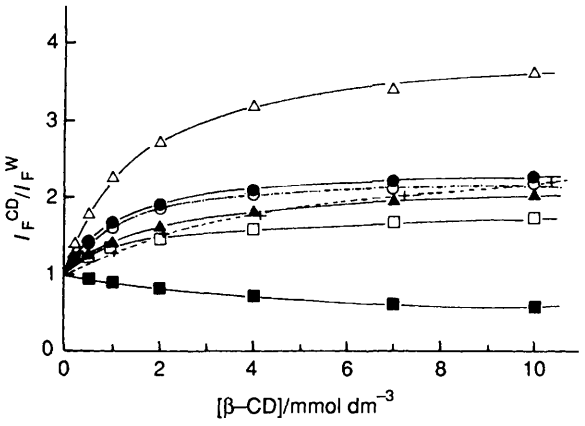


Fig. 1 Dependence of the relative fluorescence intensities of 1.0×10^{-5} mol dm^{-3} NADH analogue solutions on β-CD concentration. The fluorescence intensities were measured at wavelengths of maximum emission from β-CD-free solutions of the respective compounds (○, **1a**; ●, **1b**; △, **1c**; ▲, **1d**; □, **1e**; ■, **1f**; +, **4**). Data for compounds **2** and **3**, which show a similar trend to those of substrate **1a**, are omitted for clarity.

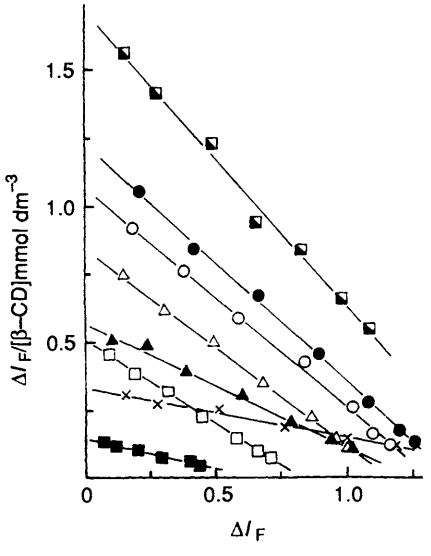


Fig. 2 Benesi–Hildebrand plots [eqn. (3)] of NADH analogues/β-CD inclusion complexation. The sign of the *x*-co-ordinate for substrate **1f** is reversed. Both *x* and *y* scales for substrate **1c** are multiplied by 0.4. The fluorescence intensities from β-CD-free solutions are normalized to 1.0 for all compounds. Symbols as for Fig. 1 except ◪, **3**.

XDHP at its absorption maximum near 350 nm as observed with a B/L Spectronic 21 spectrophotometer. Conditions of the initial reaction mixtures were: [XDHP] 5.0×10^{-5} mol dm^{-3}; [HCl] $(0.1–10) \times 10^{-3}$ mol dm^{-3} for hydration reactions; pH 5.0 with cacodylate buffer, and [Cu^{2+}] $(0.0–1.0) \times 10^{-3}$ mol dm^{-3} for copper(II) ion oxidation reactions; pH 9.0 with borate buffer, [$K_3Fe(CN)_6$] 5.0×10^{-4} mol dm^{-3}, and [$K_4Fe(CN)_6$] $(2–8) \times 10^{-4}$ mol dm^{-3} for hexacyanoferrate(3−) ion oxidation reactions. The concentration of β-CD was varied from 4.0×10^{-4} to 1.0×10^{-2} mol dm^{-3}.

Under the experimental conditions, disappearance of NADH analogues follows pseudo-first-order kinetics with respect to XDHP and the rate constant (k_φ) is determined from a plot of absorbance data against time from eqn. (1) where A_t and $A_{t+\Delta t}$ are the absorbance values at the monitoring wavelength at time t and $t + \Delta t$, respectively.

$$\ln (A_t - A_{t+\Delta t}) = -k_\varphi t + \ln [1 - \exp(-k_\varphi \Delta t)] + \text{constant} \quad (1)$$

Results

Fluorimetric Study on the Complexation between NADH Analogues and β-CD.—NADH analogues **1**–**4** fluoresce in aq. solution with an emission maximum near 460 nm. Upon addition of β-CD, enhancement of fluorescence intensity and a slight blue shift of the emission maximum (~10 nm) are observed for all NADH analogues except **1f**: the fluorescence intensity of compound **1f** rather *decreases* with increasing concentration of β-CD. In Fig. 1 we plot the quotient of emission intensity of NADH analogues in the presence of β-CD to that in the absence of β-CD as a function of the β-CD concentration.

The change in the fluorescence spectra of NADH analogues caused by β-CD reflects association between NADH analogues and β-CD. The solute entry- and exit-rate constants into and from β-CD are usually on the order of 10^7 dm^3 mol^{-1} s^{-1} and 10^4 s^{-1}, respectively,[13] whereas the fluorescence lifetime of NADH in aq. medium is 0.4 ns.[14] Therefore the observed effects of β-CD on the fluorescence spectra of NADH analogues are attributed to ground-state association.

If NADH analogues, XDHP, form 1:1 complexes with β-CD [eqn. (2)] the change in fluorescence intensity (ΔI_F) at a given

$$\text{XDHP} + \text{β-CD} \overset{K}{\rightleftharpoons} \text{XDHP–β-CD} \quad (2)$$

wavelength is proportional to the concentration of the complex, [XDHP–β-CD], and ΔI_F is related to the total concentration of β-CD, $[\text{β-CD}]_t$ by a Benesi–Hildebrand-type equation [eqn. (3)] under the stipulation that $[\text{XDHP}]_t \ll [\text{β-CD}]_t$[15,16]

$$\Delta I_F/[\text{β-CD}]_t = K(\Delta I_F)_{CD} - K\Delta I_F \quad (3)$$

where K is the association constant and $(\Delta I_F)_{CD}$ is the maximum change in fluorescence intensity when all of the NADH analogue molecules form the complex with β-CD. Plots of experimental data according to equation (3) are shown in Fig. 2 and give good straight lines with a coefficient of correlation better than 0.998. Linearity of the plots indicates that the assumption of 1:1 stoichiometry for the complexes is valid. The association constants and $(\Delta I_F)_{CD}$-values were calculated from the plots. The results are summarized in Table 1.

Efforts were also made to find any evidences of complexation of 1-benzyl-3-carbamoylpyridinium chloride (BNA^+ Cl^-), the oxidized form of BNAH **1a**, with β-CD. Neither the absorption spectrum of BNA^+ nor the emission quenching of $Ru(bpy)_3^{2+}$ (bpy denotes 2,2′-bipyridine) by BNA^+ in aq. solution are affected by the presence of as high as 15 mmol dm^{-3} β-CD (data not shown). These results strongly suggest that, unlike BNAH, the BNA^+ cation does not form an inclusion complex with β-CD to any detectable extent.

Effects of β-CD on the Hydration of NADH Analogues.—NADH analogues are known to undergo a proton-catalysed hydration reaction.[12,17] The reaction obeyed pseudo-first-order kinetics [equation (1)] with respect to NADH analogues regardless of the presence of β-CD. However, the reaction rate slows as the concentration of β-CD increases. The apparent second-order rate constants (k_H) for the hydration reaction were calculated by dividing the pseudo-first-order rate constants by the concentration of HCl. The k_H-values are independent on the concentration of HCl, as in β-CD-free solutions. Fig. 3 shows the quotients of the rate constants for compounds **1a**, **1b**, **1f** and **4** taken in the presence of β-CD relative to those in the absence of β-CD, k_H/k_H°, as a function of [β-CD]. (For k_H°-values, see

Table 1 Association constants (K) of NADH analogues with β-CD, enhancement of fluorescence intensity (I_F^{CD}/I_F^{w}) of NADH analogues upon complexation with β-CD, and the second-order rate constants ($k_H°$) for proton-catalysed hydration of NADH analogues in β-CD-free solutions at 25 °C

Compd.	X	Y	K/dm^3 mol^{-1}	$(I_F^{CD}/I_F^{w})^c$	$k_H°$/dm^3 mol^{-1} s^{-1}
1a	$CONH_2$	$PhCH_2$	810 (970)[a] (850)[b]	2.32	16
1b	$CONH_2$	p-MeC_6H_4	880 (870)[a]	2.40	1.1
1c	$CONH_2$	p-$MeOC_6H_4$	730 (720)[a]	3.88	1.5
1d	$CONH_2$	Ph	460	2.23	(1.1)[d]
1e	$CONH_2$	p-ClC_6H_4	620	1.82	(0.43)[d]
1f	$CONH_2$	p-NCC_6H_4	240 (310)[a]	0.38	0.033
2	$CSNH_2$	$PhCH_2$	780	2.23	(17)[e]
3	CO_2Me	$PhCH_2$	1100	2.57	(5.7)[e]
4	Ac	$PhCH_2$	180 (210)[a]	2.80	(0.48)[e]

[a] Determined from kinetic data for hydration reactions. [b] From results of copper(II) ion oxidation. [c] Maximum enhancement upon complete complexation. [d] Taken from ref. 17(*c*), measured in 2% propan-2-ol–98% water at 30 °C. [e] Taken from ref. 12, measured at 30 °C.

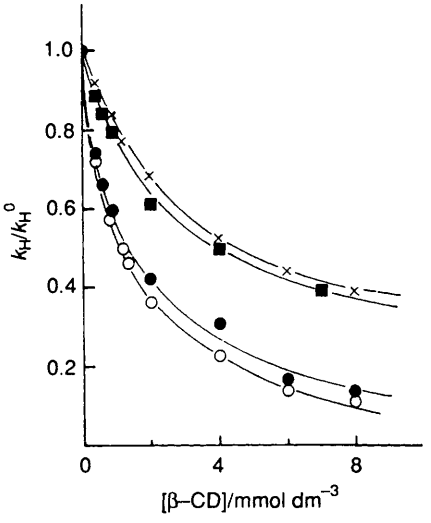


Fig. 3 Effects of β-CD on the proton-catalysed hydration. The $k_H°$-values are given in Table 1. Symbols as for Fig. 1.

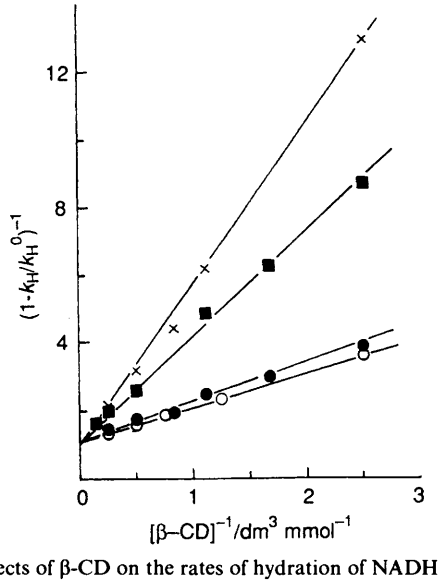


Fig. 4 Effects of β-CD on the rates of hydration of NADH analogues plotted according to eqn. (4). Symbols as for Fig. 1.

Table 1.) Fig. 3 shows clearly that the hydration reaction of NADH analogues is retarded by the presence of β-CD. The extent of inhibition of hydration differs widely among NADH analogues. A plausible explanation for the effect of β-CD on the reaction rate is that the free and the β-CD-complexed NADH analogues are hydrated with different rate constants as shown in Scheme 1, where k_H^{CD} is the second-order rate constant for

$$\begin{array}{ccc} \text{XDHP} + \beta\text{-CD} & \overset{K}{\rightleftharpoons} & \text{XDHP-}\beta\text{-CD} \\ {\scriptstyle H^+/H_2O}\downarrow {\scriptstyle k_H°} & & {\scriptstyle H^+/H_2O}\downarrow {\scriptstyle k_H^{CD}} \\ \text{product} & & \text{product} \end{array}$$

Scheme 1

hydration of XDHP complexed with β-CD. Assuming rapid equilibrium between XDHP and β-CD, then k_H, $k_H°$, k_H^{CD} and K are related by eqn. (4).

$$(1 - k_H/k_H°)^{-1} = (1 - k_H^{CD}/k_H°)^{-1} + \{(1 - k_H^{CD}/k_H°)K\}^{-1}[\beta\text{-CD}]^{-1} \quad (4)$$

As the total concentration of β-CD, $[\beta\text{-CD}]_t$, is more than 8 times the initial concentration of NADH analogues, [β-CD] can be replaced by $[\beta\text{-CD}]_t$. The plots of kinetic data (Fig. 3) according to equation (4) are shown in Fig. 4. Good linearity in Fig. 4 implies that Scheme 1 is valid. For all NADH analogues investigated the intercepts of the plots were very close to 1. This indicates that the rate of hydration of NADH analogues complexed with β-CD is virtually zero, *i.e.* $k_H^{CD} \cong 0$, regardless of the substituents on the dihydropyridine. Reciprocal slopes of the plots were taken as K. The K-values determined by this method are included in Table 1.

The association constants of NADH analogues with β-CD determined by fluorimetric and kinetic methods are in good agreement, when one considers that the relative uncertainty of K-values is ±10%.

Effect of β-CD on the Copper(II) Ion Oxidation Reaction of Compound **1a**.—Copper(II) ion oxidizes NADH analogues in aq. solution. In the presence of dissolved molecular oxygen, the reaction follows first-order kinetics with respect to both NADH analogue and Cu^{2+}, indicating a catalytic role for copper(II).[18] The oxidation reaction proceeds in parallel with the aforementioned proton-catalysed hydration reaction. The pseudo-first-order rate constant, k_{obsd}, for the disappearance of NADH analogues in the presence of Cu^{2+} in acidic aq. medium is expressed as eqn. (5).[18]

$$k_{obsd} = k_H[H^+] + k_{Cu}[Cu^{2+}] \quad (5)$$

The pseudo-first-order rate constants, k_{obsd}, for disappearance of compound **1a** were determined at pH 5 from solutions containing various concentrations of β-CD. The results are shown in Fig. 5 as a function of Cu^{2+} concentration.

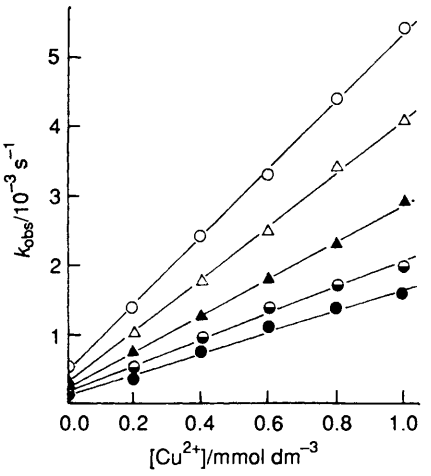


Fig. 5 Plots of pseudo-first-order rate constants of copper(II) ion oxidation of compound **1a** at various concentrations of β-CD as a function of [Cu^{2+}]. pH of the solutions was 5.0. [β-CD]/mmol dm^{-3} = 0.0 (○), 0.3 (△), 1.0(▲), 2.0 (◒) and 3.0 (●).

Table 2 Pseudo-first-order oxidation rate constants ($10^2 k_\psi$/s^{-1}) of 5.0 × 10^{-5} mol dm^{-3} BNAH **1a** by 5.0 × 10^{-4} mol dm^{-3} $Fe(CN)_6^{3-}$ at various concentrations of $Fe(CN)_6^{4-}$ in the absence and presence of 2.0 mmol dm^{-3} β-CD

	[$Fe(CN)_6^{4-}$]/10^{-3} mol dm^{-3}			
[β-CD]/10^{-3} mol dm^{-3}	0.2	0.4	0.6	0.8
0.0	2.8	1.9	1.5	1.3
2.0	1.1	0.78	0.66	0.53
		(k_ψ^{CD}/k_ψ^{W})[a]		
	0.39	0.41	0.44	0.41
		av. 0.41		

[a] The ratio of k_ψ-values in the presence of 2.0 mmol dm^{-3} β-CD relative to the corresponding values in the absence of β-CD.

The intercept and slope of each plot in Fig. 5 correspond to the pseudo-first-order rate constant for the hydration reaction, $k_H[H^+]$, and the second-order rate constant for the copper(II) ion oxidation reaction, k_{Cu}, of substrate **1a** at the corresponding concentration of β-CD, respectively. Dependence of k_{Cu} on the concentration of β-CD follows closely the trend observed for the second-order hydration rate constant of the corresponding compound given in Fig. 3. A plot of k_{Cu}/k_{Cu}°, where k_{Cu}° is k_{Cu} in the absence of β-CD, according to an equation equivalent to equation (4) was satisfactorily linear (plot not shown) and the intercept was 1. The association constant of compound **1a** with β-CD calculated from the plot was 850 dm^3 mol^{-1}, which agrees well with that from fluorescence titration or hydration reaction data (Table 1) within the limits of experimental error. These results clearly indicate that the NADH analogue included in the β-CD cavity is well protected against copper(II) ion oxidation, as well as against hydration.

Effect of β-CD on the Hexacyanoferrate(3 −) Ion Oxidation of Compound **1a**.—The reaction of 1,4-dihydronicotinamides with $Fe(CN)_6^{3-}$ is first-order in both [$Fe(CN)_6^{3-}$] and [substrate] and is inhibited by $Fe(CN)_6^{4-}$, giving a linear relationship between the reciprocal of the pseudo-first-order rate constant and [$Fe(CN)_6^{4-}$].[19] We have carried out the reaction of 5.0 × 10^{-5} mol dm^{-3} **1a** with 5.0 × 10^{-4} mol dm^{-3} $Fe(CN)_6^{3-}$ in pH 9 borate buffer containing various concentrations of $Fe(CN)_6^{4-}$ in the absence and in the presence of 2.0 mmol dm^{-3} β-CD. As in β-CD-free solution, the change in absorbance of the reaction mixtures in 2.0 mmol dm^{-3} β-CD solutions followed pseudo-first-order kinetics, equation (1) (plots not shown). The rate constants for the disappearance of substrate **1a** were determined from the plots and are summarized in Table 2.

Taking the association constant of substrate **1a** with β-CD as 900 dm^3 mol^{-1}, the fraction of **1a** uncomplexed with β-CD at 2.0 mmol dm^{-3} β-CD is 0.36. This value is close to the observed quotient of the pseudo-first-order rate constants, 0.41, for the reaction of compound **1a** with $K_3Fe(CN)_6$ in the presence of 2.0 mmol dm^{-3} β-CD relative to that in the absence of β-CD. Therefore, the inhibitory effect of β-CD against hexacyanoferrate(3 −) ion oxidation of compound **1a** is comparable with that for other reactions presented in the previous sections.

Discussion

The enhancement of the fluorescence intensity concomitant with the spectral blue shift of NADH analogues, except **1f**, by inclusion complexation with β-CD is a general feature observed with a wide variety of hydrophobic molecules or ions.[20] This is ascribed, in part, to a decrease in the non-radiative decay processes by the elimination of water molecules surrounding the fluorophore and by oxygen quenching upon complexation. Unlike other NADH analogues, the fluorescence intensity of 1-(*p*-cyanophenyl)-1,4-dihydronicotinamide **1f** is reduced in the presence of β-CD. This is similar to the phenomenon reported for 1-cyanonaphthalene[21] and can be attributed to a decrease in electron transfer from the cyano group to the aromatic ring in the excited singlet state of the fluorescent molecules complexed by β-CD.[22]

The strong absorption band of 1,4-dihydropyridines near 350 nm was assigned to the n–π* transition of the dihydropyridine moiety.[23] Thus the fluorescence emission of NADH analogues can be ascribed to the reversal of this transition. The great similarity of emission behaviour among the NADH analogues investigated in this study, despite the large difference in the nature of the substituents on the dihydropyridine ring, supports this. The large change in fluorescent properties as well as in chemical reactivity of the NADH analogues upon complexation with β-CD indicates that the dihydropyridine ring is preferentially included in the β-CD cavity, leaving the 1-substituent (phenyl or benzyl group) protruding outside from the cavity. Harata *et al.* reported an X-ray crystallographic structure of β-CD–nicotinamide complex, in which nicotinamide is included in the β-CD cavity and both carbonyl oxygen and amide nitrogen form hydrogen bonds with hydroxy groups of the host molecule.[11]

The present study shows that the complex-formation constants between β-CD and NADH analogues are very dependent upon the nature of the 1- and 3-substituent of the NADH analogues. Various factors contribute to the stability of inclusion complexes with cyclodextrins.[1,24,25] Dipolar or van der Waals interactions are often suggested to be the main driving forces.[24,25] Although the correlation is not excellent, our results (Table 1) show a clear tendency for larger complex-formation constants as the 1- or 3-substituent becomes less electron withdrawing and/or more polarizable. Among NADH analogues investigated in this study, compound **3** forms the most stable complex with β-CD. This seems to indicate that the ester group of compound **3** is located inside the cavity of β-CD and that the ether oxygen of this substrate forms hydrogen bonds with hydroxy groups of β-CD in similar fashion to those of the amide hydrogen, as depicted in an X-ray crystallographic work of β-CD–nicotinamide complex.[11] The possibility of hydrogen bonding seems to be supported by the observation that the complex of compound **4**, which does not bear an additional hydrogen-bonding site

besides a carbonyl oxygen, is the least stable of those complexes examined here.

As mentioned earlier, β-CD protects NADH analogues against reactions with H^+, Cu^{2+} and $Fe(CN)_6^{3-}$ by including the substrate molecule in its cavity. Two possible mechanisms for the inhibitory effects of β-CD may be suggested. One is steric exclusion of the reactant ions from the substrates by β-CD as suggested for effects of cyclodextrins in the oxidation of Methyl Orange by singlet oxygen.[26] The other is destabilization of the transition state or reaction intermediates, which bear a net charge and thus for which β-CD complexes are energetically disfavoured. This view is supported by our failure to observe inclusion complexation of BNA^+ into β-CD.

There are reports of many systems for which cyclodextrins or their derivatives accelerate chemical reactions.[1,2] For these, formation of ternary complexes and/or *direct* involvement of hydroxy or functional groups of cyclodextrins must be taken into consideration. *In vivo*, retardation of the deactivating hydration of coenzyme NADH and concomitant acceleration of reductions by NADH may take place through the interaction of the coenzyme with NADH-dependent enzymes. The present observation of excellent binding of NADH analogues by β-CD and efficient protection of the coenzyme model compounds against reactions by species in a bulk aq. phase may give promise of application of cyclodextrins and their derivatives as well as NADH analogues to a variety of biomimetic reactions as well as to investigation of NADH-dependent enzymes.

Acknowledgements

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