sensitive method of observing the oxidation of polybutadiene and other diene rubbers.

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Coenzyme Models. 10. Rapid Oxidation of NADH by a Flavin Immobilized in Cationic Polyelectrolytes

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ABSTRACT: The title flavin rapidly oxidizes NADH, the observed enhancement being of 460–4650-fold compared with 3-methyltetra-*O*-acetylriboflavin. Analysis of the kinetic data at 30 °C established that the reaction proceeds according to the Michaelis–Menten kinetics at low ionic strength ($\mu = 0.02$: K_m = ca. 10^{-5} M, $k_{\text{cat.}} = 0.06$–$0.37\ \text{s}^{-1}$) and according to the simple second-order kinetics at high ionic strength ($\mu = 0.3$), the largest rate difference being 342-fold. On the other hand, the oxidation of 1-benzyl-1,4-dihydronicotinamide, a NADH model compound, was not accelerated by the use of the title flavin. It is concluded, therefore, that the formation of the polymeric flavin–NADH complexes due to the electrostatic interaction is responsible for the marked rate enhancement. This is the first example that the oxidation of NADH is facilitated in the nonenzymatic system.

Of many flavin coenzyme dependent reactions, the oxidation–reduction reaction couple between NADH (reduced form of nicotinamide–adenine dinucleotide) and flavoprotein is of special interest.[2,3] Although the reaction occurs in nonenzymatic systems, NADH by itself acts as a less reactive reducing agent for flavins than simple NADH model compounds such as 1-alkyl-1,4-dihydronicotinamide.[2,3] It is clear, therefore, that the environment of enzymes (e.g., FMN oxidoreductase) is performing the role of catalyst.

We recently found that rates and equilibrium constants for the addition of cyanide and sulfite ions to poly[1-(4-vinylbenzyl)nicotinamide chloride] (cationic polyelectrolyte) are markedly enhanced in comparison to the monomeric analogue.[4,5] Since the association constant can be correlated with the reactivity of NAD$^+$ (and analogues),[6] it is suggested that the nicotinamide group in cationic polyelectrolytes would serve as an excellent oxidizing agent, especially for the oxidation of anionic species. With the expectation to develop efficient oxidizing agents for flavin-mediated reaction systems, we synthesized the following flavin-containing polymers and assessed the oxidation of NADH(polyanion) and the model compound, 1-benzyl-1,4-dihydronicotinamide (BzlNicH) (eq 1). We found that the oxidation of NADH is remarkedly accelerated by the use of a flavin immobilized in cationic polyelectrolytes and that the reaction proceeds according to the Michaelis–Menten kinetics. To our knowledge this is the first

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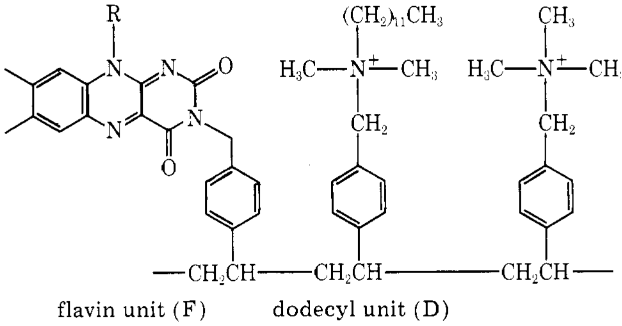
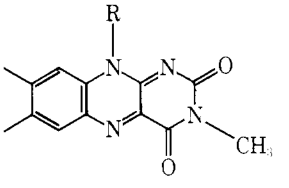
Table I
Composition of Flavin-Containing Polymers and λ_{max} and ϵ of Flavins (30 °C)

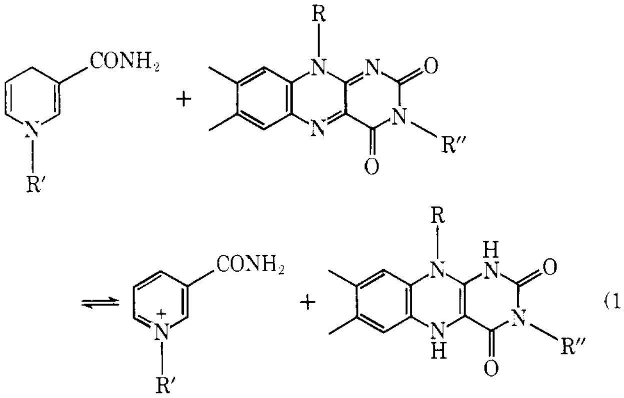
Polymer[a]	Unit (mol %)					λ_{max},	
	Flavin	Dodecyl	Methyl	Pyridine	Nicotinamide	nm	$\epsilon \times 10^{-3}$
F-D-0	5.0	0	82			460	5.98
F-D-7	5.3	7	86			455	7.98
F-D-12	5.0	12	70			454	8.15
F-D-22	5.3	22	68			453	6.85
F-Py-72	5.2			72			
F-Nic-59	5.2				59		
3-MeF						447	12.2

[a] The abbreviation F-D-22 stands for the polymer containing 22 mol % of the dodecyl group.





3-MeF



R = tetra-*O*-acetylribosyl, R′ = benzyl,
R″ = methyl (3-MeF) or polymer

example that the reaction between NADH and flavin is facilitated in the nonenzymatic system.

Experimental Section

Materials. Tetra-*O*-acetylriboflavin and 3-methyltetra-*O*-acetylriboflavin (3-MeF) were prepared according to the method of Hemmerich,[7] and were identified by NMR, elemental analysis, and melting points. NADH is a kind gift from Kyowa Hakko Kogyo Co. 1-Benzyl-1,4-dihydronicotinamide (BzlNicH) was prepared from 1-benzylnicotinamide chloride and sodium dithionite,[8] mp 110–112 °C (lit.[8] mp 110–112 °C). Poly(styrene) (M_w = 7560) was treated with chloromethyl methyl ether in the presence of $ZnCl_2$ in 1,2-dichloroethane at 60 °C for 4 h.[9] The characterization of the recovered polymers by NMR and elemental analysis showed that 1.0 chloromethyl group is incorporated per monomeric unit of poly(styrene). Anal. Calcd for C_9H_9Cl: C, 70.83; H, 5.94. Found: C, 70.47; H, 5.90.

Tetra-*O*-acetylriboflavin was allowed to react with excess poly(chloromethylstyrene) in dimethylformamide in the presence of K_2CO_3.[7] The flavin content in the recovered polymer was calculated based on the C, N analysis. For example, the elemental analysis data for a precursor of F-D-7 and F-D-22 are: C, 67.98; N, 1.64. The flavin content can be thus estimated to be 5.3 mol %.

The elemental analysis of the recovered polymer showed that tetra-*O*-acetylriboflavin in feed reacted with polymer almost quantitatively. After further reaction with *N*,*N*-dimethyldodecylamine (48 h in dimethylformamide at room temperature) and trimethylamine (48 h in 80 vol % aqueous dimethylformamide at room temperature), the polymers were purified by extensive dialysis. Similarly the reactions with pyridine and nicotinamide were conducted in dimethylformamide for 50 h at room temperature and were purified by extensive dialysis. The content of the substituents was evaluated by elemental analysis. The composition of flavin-containing polymers is summarized in Table I, together with λ_{max} and ϵ_{max} of flavin incorporated.

Kinetics. As reported earlier,[2,10] the O_2 reoxidation of reduced flavin formed during the reduction by NADH (and model compounds) is so instantaneous that the concentration of flavin is obviously constant as long as O_2 resides in the reaction medium (i.e., $k_{cat.}$[polymer F·NADH] $\ll$ $k_{reoxidation}[O_2]$[polymer FH_2] in eq 2). Thus, the rates determined in aerobic solution by following the decrease in the absorption of dihydronicotinamide are first order with respect to dihydronicotinamide. More recently, the flavin oxidation of dihydronicotinamide has been reported to proceed via preequilibrium charge-transfer complexes. The aerobic rate constants are greater than the anaerobic rate constants when the concentration of the charge-transfer complexes is appreciably enhanced.[11] However, the dissociation constants for the charge-transfer complexes are so large (in the order of 0.1 M)[11] that, if the concentrations of both reagents are maintained at much less that 0.1 M, complex formation would be negligible.[12] Throughout our experiments, the concentrations of the flavins and the dihydronicotinamide were not much greater than 10^{-4} M, and any evidence for complex formation was not obtained. In fact, the aerobic and anaerobic rate constants agreed within experimental error (vide post). A similar kinetic situation has been reported by Kaiser et al.[12] for the catalytic action of "flavopapain", semisynthetic enzyme. Thus, the kinetic study was carried out under the aerobic conditions: 30 °C, pH 9.0 with 0.02 M borate buffer, and μ = 0.02 with KCl (unless otherwise stated). The wavelengths employed were 338 nm for NADH and 357 nm for BzlNicH.

The reaction of polymeric flavin and NADH was performed in the presence of excess flavin. When excess NADH was employed, the turbidity (probably due to the formation of polyion-type complexes) appeared. Thus, the Michaelis–Menten kinetics in the presence of excess NADH could not be assessed.

Miscellaneous. The polarographic half-wave potentials ($E_{1/2}$) were determined at room temperature with Yanagimoto P8 polarographic equipment.

Results and Discussion

Oxidation of BzlNicH. Dihydronicotinamide concentration as a function of time gave good pseudo-first-order plots under all conditions used in this work up to 70% reaction. The pseudo-first-order rate constants (k_{obsd}) plotted against the concentration of the flavin unit in polymer or 3-MeF gave straight lines which pass through the origin ([flavin] = (2–10) $\times 10^{-5}$M, [BzlNicH] = 1.62×10^{-5} M). Therefore, the reaction is first order with respect to flavin and BzlNicH.

Table II indicates that the second-order rate constants, k_2, for the polymeric flavins are greater by factors of 6 to 7 than that for 3-MeF. Gascoigne and Radda[13] have reported that

Table II
Kinetic Parameters for the Flavin Oxidation of BzlNicH and NADH[a]

		BzlNicH	NADH			
Polymer	$E_{1/2}$, V	k_2, $M^{-1} s^{-1}$	$k_{cat.}$, s^{-1}	$K_m \times 10^5$, M	$k_{cat.}/K_m$, $M^{-1} s^{-1}$	k_2, $M^{-1} s^{-1}$
F-D-O	−0.427	190	0.062	2.61	2 380	
D-D-7	−0.433	201	0.189	1.32	14 300	
F-D-12	−0.438	231	0.142	0.947	15 000	
F-D-22	−0.441	201 (208)[c]	0.373	1.54	24 200	
F-D-22[b]		389 (404)[c]				79.0
F-Py-72		123 (129)[c]				
F-Nic-59		85.7				
3-MeF	−0.492	32.4				5.2

[a] $\mu = 0.02$ with KCl. [b] $\mu = 0.3$ with KCl. [c] Determined under the anaerobic conditions.

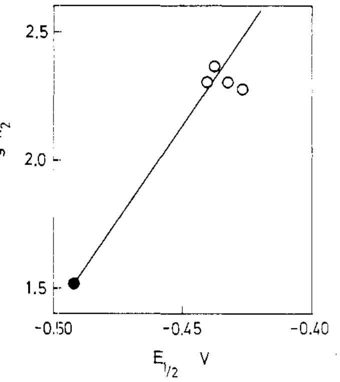


Figure 1. Plot of log k_2 vs. $E_{1/2}$ for the flavin oxidation of BzlNicH. The filled circle indicates the plot for the 3-MeF oxidation. The solid line with the slope of 15.1 is depicted so as to pass this circle.

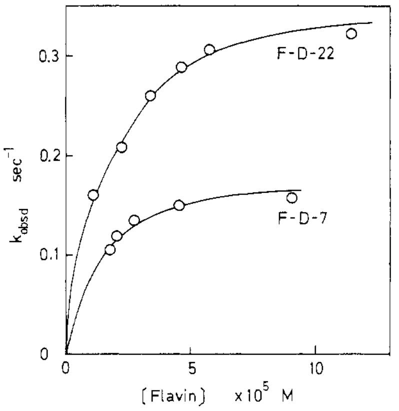


Figure 2. Plots of k_{obsd} vs. flavin concentration for the flavin oxidation of NADH. [NADH] = 0.831×10^{-5}M.

the logarithm of the k_2 values is linearly correlated with the polarographic half-wave potentials ($E_{1/2}$) with a slope of 15.1 (= log $k_2/E_{1/2}$). As shown in Figure 1, the experimental data sets of log k_2 vs. $E_{1/2}$ are connected with a straight line with the slope 15.1. Therefore, the rate augmentation observed can be ascribed to the shift of $E_{1/2}$.

The polymers quaternized by pyridine and nicotinamide (F-Py-72, F-Nic-59) showed smaller catalytic efficiencies (Table II). The rate constants determined under the anaerobic conditions are in agreement with the aerobic rate constants within experimental error (less than 4%).

Oxidation of NADH. The oxidation of NADH by 3-MeF was also confirmed to be first order in both reagents ($k_2 = 5.2$ M^{-1}/s^{-1}, Table II). As expected,[2,3] the k_2 value for the 3-MeF oxidation of NADH amounts only to one-sixth of that for the 3-MeF oxidation of BzlNicH. On the other hand, the reaction rates for the oxidation of NADH by polymeric flavins showed a saturation tendency at [flavin] = ca. 5×10^{-5} M (Figure 2). Assuming that 1:1 complexes are formed between the flavin unit and NADH, the double reciprocal plots of k_{obsd} vs. flavin concentration (Lineweaver–Burk plots[14]) provided good straight lines (r = 0.98–0.99), indicating that the reaction proceeds according to the Michaelis–Menten kinetics (eq 2).

$$\begin{tikzcd} & \text{polymer F}\cdot\text{NADH} \arrow[dr, "k_{cat.}"] & \\ \text{polymer F + NADH} \arrow[ur, leftrightarrow, "K_m"] & & \text{polymer FH}_2 + \text{NAD}^+ \arrow[ll, bend left, "O_2"] \end{tikzcd} \qquad (2)$$

Thus, $k_{cat.}$ and K_m were determined by the least-squares method from the slope and the intercept. The results are summarized in Table II. The examination of Table II reveals that the overall catalytic efficiency ($k_{cat.}/K_m$) of the polymeric systems is enhanced by factors of 460–4650-fold, compared with k_2 for 3-MeF. It is clear that the remarkable rate augmentation is derived from the efficient binding of NADH, conceivably due to the formation of polyion complexes.[15] It is interesting to note that the Michaelis constants of NADH with the corresponding apoenzymes are not much smaller, i.e., (0.2–1.0) $\times 10^{-5}$ M for alcohol dehydrogenase.[16]

Strauss and co-workers[17] previously reported for quaternized poly(vinylpyridines) that the transition from polyelectrolyte to polymer micelle is observed at 10–13 mol % of the dodecyl group content. The polymer micelle provides the hydrophobic region stronger than the conventional micelle[18,19] and efficiently binds polyanionic species.[20-22] Table II shows that F-D-22 exhibits more excellent binding (smaller K_m) and catalytic (greater $k_{cat.}$) tendencies than F-D-O, but the difference is rather small. Conceivably, the backbone of quaternized poly(chloromethylstyrene) is hydrophobic relative to quaternized poly(vinylpyridine), and the incorporated dodecyl group causes a little influence on the overall hydrophobicity of quaternized poly(chloromethylstyrene).

In the conventional micelle system, we have found that a flavin (and analogues) present in the hydrophobic region pocesses smaller ϵ_{max} and red-shifted λ_{max} values.[23,24] In some cases,[23,24] a new shoulder appears at 460–470 nm which is characteristic of flavins in organic solvents. Though the flavin immobilized in quaternized poly(chloromethylstyrene) did not give rise to such a shoulder, ϵ_{max} and λ_{max} values in Table I suggest that the flavin resides in the relatively hydrophobic region. On the other hand, the influence of the dodecyl group content on ϵ_{max} and λ_{max} values is again insignificant.

Influence of Ionic Strength. In Figure 3, pseudo-first-order rate constants are plotted as a function of ionic strength (KCl). The k_{obsd} value for the oxidation of BzlNicH by F-D-22 increased gradually with increasing ionic strength. On the other hand, the oxidation rate of NADH was markedly suppressed by increasing the ionic strength, and the simple sec-

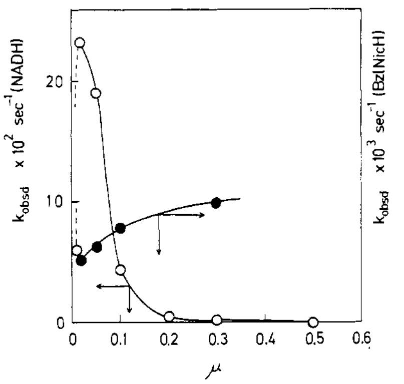


Figure 3. k_{obsd} for F-D-22 plotted as a function of ionic strength (KCl). [NADH] = 1.63×10^{-5} M, [BzlNicH] = 1.134×10^{-4} M, [flavin] in F-D-22 = 2.55×10^{-5} M.

ond-order behavior ($k_2 = 79.0\ M^{-1}\ s^{-1}$) was observed at μ = 0.3. The largest rate decrease caused by the increase in ionic strength was 342-fold. It is clear that NADH is bound onto F-D-22 mainly due to the electrostatic interaction and that the increase in ionic strength enforces the change in the reaction path from the preequilibrium binding of NADH to the simple second-order type. Strangely, the reaction rate was retarded by the further decrease in ionic strength (μ = 0.01, Figure 3). We believe that the adenine moiety of NADH is responsible for this peculiar behavior, but the details are not clear at present.

Concluding Remark. The present study established that NADH is bound to the cationic polyelectrolyte in the order of 10^{-5} M and that the efficient oxidation ensues by the immobilized flavin. The highly efficient oxidoreduction system developed is interesting not only from the standpoint of a model study of the corresponding enzymes but also in the NAD^+ recycling problem in the asymmetric synthesis of alcohol dehydrogenase.[25-27] Finally, the proposed concept may be applicable more generally to the oxidation of polyanionic species. For example, we have found that glutathione, a biological cofactor, undergoes the rapid oxidation by a flavin immobilized in cationic polyelectrolytes.

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Propagation and Depropagation Rates in the Anionic Polymerization of ε-Caprolactone Cyclic Oligomers

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ABSTRACT: The rate of formation of ε-caprolactone cyclic oligomers has been studied in the anionic polymerization–depolymerization equilibrium system initiated by lithium *tert*-butoxide in tetrahydrofuran at 0 °C. The apparent rate constants for propagation increased with the ring size from the dimer to the hexamer, while those for depropagation remained almost constant or very slightly decreased with the ring size. This is a kinetic consequence for the cyclization equilibrium constant which decreased with increasing ring size. ε-Caprolactone monomer itself was exceedingly far more reactive than the cyclic oligomers to be hardly detected at equilibrium.

Recently[1] we have shown that the anionic polymerization of ε-caprolactone with potassium *tert*-butoxide in tetrahydrofuran provides a thermodynamically controlled, living ring-chain equilibrium system. As expected from the Jacobson–Stockmayer theory,[2-4] the product distribution was essentially determined by the entropy term, the lower cyclics being more favored over the linear polymers with increasing dilution. Although the equilibration was so fast to be complete

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