Multicenter Organic Redox Systems Composed of Bis(1,4-dihydronicotinamides): Optimal Conformation for Intramolecular Electronic Interaction[1]

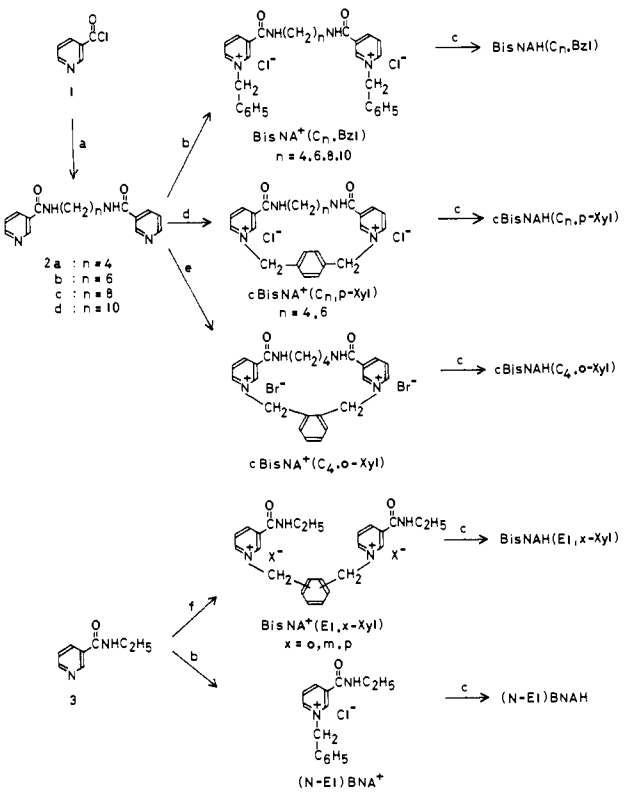
Yukito Murakami,* Yasuhiro Aoyama,[2] Jun-ichi Kikuchi, and Koji Nishida

Contribution No. 647 from the Department of Organic Synthesis, Faculty of Engineering, Kyushu University, Fukuoka 812, Japan. *Received December 7, 1981*

Abstract: Bis(1,4-dihydronicotinamides) were prepared as dimers of 1-benzyl-3-(*N*-ethylcarbamoyl)-1,4-dihydropyridine [(*N*-Et)BNAH], which are structurally classified into three categories: flexible [BisNAH(C_n,Bzl)], partially rigid [BisNAH(Et,*x*-Xyl)], and doubly linked, rigid, and cyclic dimers [cBisNAH(C_n,*p*-Xyl) and cBisNAH(C_4,*o*-Xyl)]. Bis(1,4-dihydronicotinamides) of another family regarded as singly [BisNAH(C_6,Pr) and BisNAH(Pr,C_6)] and doubly linked [cBisNAH(C_6,C_6)] dimers of 1-propyl-3-(*N*-propylcarbamoyl)-1,4-dihydropyridine [(N-Pr)PNAH] were also synthesized. The reactivity of bis(dihydronicotinamides) in dichloromethane was subjected to change to a wide extent depending upon their molecular structures in the reduction of hexachloroacetone. Among bis(dihydronicotinamides) regarded as dimers of (*N*-Et)BNAH, cBisNAH(C_4,*o*-Xyl) was the most reactive. The overall reactivity order with respect to this family followed the sequence: cBisNAH(C_4,*o*-Xyl) > BisNAH(C_n,Bzl) (n = 4, 6) > BisNAH(Et,*o*-Xyl) > cBisNAH(C_4,*p*-Xyl) ≃ BisNAH(C_8,Bzl) ≃ BisNAH(Et,*m*-Xyl) > cBisNAH(C_6,*p*-Xyl) ≃ BisNAH(C_{10},Bzl) > BisNAH(Et,*p*-Xyl) = (*N*-Et)BNAH. An effective charge-transfer interaction, which emerges from the favorable face-to-face arrangement of the two dihydronicotinamide rings in the transition state of reduction, is responsible for the kinetic enhancement. Both cBisNAH(C_4,*o*-Xyl) and BisNAH(C_n,Bzl) (n = 4, 6) may assume a close face-to-face geometry without inducing significant strain in the transition state. The prevailing reactivity of the former over the latter was attributed to an entropy effect, since the two nicotinamides in the former attain such a favorable conformation already in the ground state while those in the latter may rather take an extended geometry without mutual interaction, as confirmed by spectroscopic measurements. As for the other family of bis(dihydronicotinamides), the reactivity sequence was as follows: BisNAH(C_6,Pr) > cBisNAH(C_6,C_6) ≃ BisNAH(Pr,C_6) > (*N*-Pr)PNAH. A lower reactivity of the doubly linked bis(dihydronicotinamide) cBisNAH(C_6,C_6) was attributed to a much less favorable conformation of the nicotinamide rings involved. Molecular geometries of the present bis(dihydronicotinamides) as well as their dehydrogenated counterparts were examined by electronic and NMR spectroscopy.

Multicenter metal or metal ion systems are often very important as redox catalysts, although detailed catalytic mechanisms remain unsettled in most cases. Examples include a number of metalloenzymes containing two or more metal ions in biological systems on one hand and bi- or polynuclear metal complexes,[3] metal clusters,[4] monolayer-bound metal complexes,[5] and solid metal or metal oxides[6,7] including semiconductors[8] in artificial systems on the other. A rapidly growing area of research in redox chemistry of metal complexes concerns the preparation of well-designed binuclear metal complexes capable of multielectron transfer, such as binuclear cryptates,[9] face-to-face metalloporphyrin dimers,[10-12] and others.[13] In contrast to rich achievement with the multicenter metal complex systems, it is rather surprising that organic

Scheme I[a]



[a] Reagents: a, $H_2N(CH_2)_nNH_2$; b, $C_6H_5CH_2Cl$; c, $Na_2S_2O_4$; d, *p*-$C_6H_4(CH_2Cl)_2$; e, *o*-$C_6H_4(CH_2Br)_2$; f, *o*-, *m*-, or *p*-$C_6H_4(CH_2X)_2$ (X = Cl or Br).

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(2) Present address: Department of Material Science and Technology, Technological University of Nagaoka, Nagaoka, Niigata 949-54, Japan.

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Table I. Physical and Spectral Properties of *N,N'*-Alkylenebis(3-carbamoylpyridines)

compd	state	yield, %	mp, °C	IR,[a] cm^{-1} ν_{NH}	IR,[a] cm^{-1} $\nu_{C=O}$	IR,[a] cm^{-1} δ_{NH}	^{1}H chemical shifts, δ[b] 2-H	4-H	5-H	6-H	CONHCH_2	CH_2[c]
2a	colorless needle	54	202–203	3200	1620	1540	8.90	8.18	7.46	8.61	3.45	1.73
2b	colorless plate	74	168–170	3250	1622	1522	8.90	8.16	7.45	8.60	3.44	1.55
2c	colorless plate	80	154–158	3250	1622	1527	8.90	8.17	7.45	8.60	3.45	1.41
2d	white powder	24	144–148	3250	1625	1528	8.85	8.10	7.40	8.55	3.35	1.35

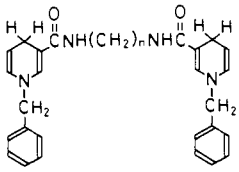
[a] KBr disk method. [b] Measured in methanol-d_4. Chemical shifts are given in ppm downfield from Me_4Si. Multiplicities: 2-H, s; 4-H, d; 5-H, m; 6-H, d; CONHCH_2, t; other methylene H's, m. [c] Other methylene protons.

multicenter systems have so far attracted little attention from the viewpoint of redox catalysis.[14] We have initiated, under such circumstances, studies on multicenter organic redox systems, which can be subjected to systematic structural modifications.

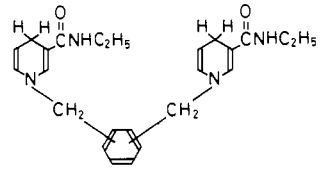
The redox reactivity of various 1,4-dihydronicotinamides has been rather extensively investigated recently in connection with the chemistry of coenzyme NAD(P)H. Thus, we intend to manipulate the reactivity of 1,4-dihydronicotinamide by introducing multicenter character into the molecule, which can be achieved by intramolecular assembly of multiple dihydronicotinamide moieties. We prepared in this work a series of closely related bis(1,4-dihydronicotinamides) along this line and investigated their reactivities in the reduction of a carbonyl substrate. The results presented herein clearly demonstrate the importance of an intramolecular charge-transfer interaction for kinetic enhancement, and the extent of such an electronic interaction is highly sensitive to molecular structures.

Results and Discussion

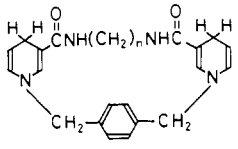
Preparation of Bis(1,4-dihydronicotinamides). A series of closely related noncyclic bis(1,4-dihydronicotinamides) (NAH-NAH's) were first prepared. Either flexible polymethylene chains of



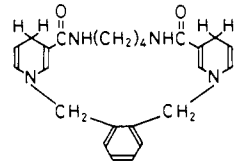
BisNAH(C_n,Bzl)
n = 4,6,8,10



BisNAH(Et,x-Xyl)
x = o,m,p



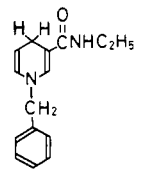
cBisNAH(C_n,p-Xyl)
n = 4,6



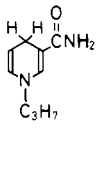
cBisNAH(C_4,o-Xyl)

varying chain length bound to amide nitrogens or rigid isomeric xylylenes bound to ring nitrogens served as bridging components to link two 1,4-dihydronicotinamide moieties. The synthetic routes are shown in Scheme I. Condensation of an α,ω-diaminoalkane with nicotinoyl chloride (**1**) followed by bisquaternization with benzyl chloride gave BisNA$^+$(C_n,Bzl), while quaternization of *N*-ethylnicotinamide (**3**) with xylylene dihalides afforded BisNA$^+$(Et,*x*-Xyl). All the bisnicotinamide salts were reduced with sodium dithionite to give the corresponding bis(1,4-dihydronicotinamides). Subsequently, several cyclic bis(1,4-dihydronicotinamides) of related structures were synthesized. The corresponding oxidated species, cBisNA$^+$(C_n,*p*-Xyl) and cBisNA$^+$(C_4,*o*-Xyl), were prepared from the precursor bis(nicotinamides) (**2a,b**) by their cyclization–bisquaternization with xylylene dihalides under high dilution conditions and subsequently reduced with sodium dithionite. The physical and spectral properties of *N,N'*-alkylenebis(3-carbamoylpyridine)s (**2**) are listed in Table I.

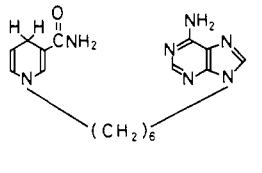
The present bis(1,4-dihydronicotinamides) are structurally classified into three categories as dimers of 1-benzyl-3-(*N*-ethylcarbamoyl)-1,4-dihydropyridine [(*N*-Et)BNAH]: flexible [BisNAH(C_n,Bzl)], partially rigid [BisNAH(Et,*x*-Xyl)], and doubly linked, rigid, and cyclic dimers [cBisNAH(C_n,*p*-Xyl) and cBisNAH(C_4,*o*-Xyl)].



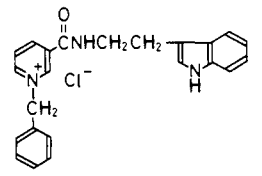
(N-Et)BNAH



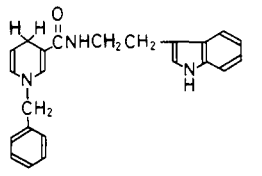
PNAH



NAH-C_6-Ad



(N-Et-1)BNA$^+$



(N-Et-1)BNAH

In addition, some bis(1,4-dihydronicotinamides) regarded as singly [BisNAH(C_6,Pr) and BisNAH(Pr,C_6)] and doubly linked [cBisNAH(C_6,C_6)] dimers of 1-propyl-3-(*N*-propylcarbamoyl)-1,4-dihydropyridine [(*N*-Pr)PNAH] were prepared by the routes shown in Scheme II.

Spectroscopic Properties of Bis(1,4-dihydronicotinamides). The ^{1}H NMR chemical shifts for the dihydronicotinamide ring protons were found to be sensitive to relative conformations of the rings (Table II). The chemical shifts for the nicotinamide protons of bis(nicotinamide) species (NA$^+$–NA$^+$) are shown in Table III and Figure 1. The space-filling CPK molecular models for cBisNAH(C_4,*o*-Xyl) and its dehydrogenated species indicate that the two nicotinamide rings assume a close *face-to-face* conformation (Figure 2a) with a perpendicular orientation of the benzene ring relative to the nicotinamide moieties, so that the 2-H protons of the nicotinamide groups are placed right on the benzene ring (Figure 2b), i.e., in the shielding zone. Consistent with this view, the resonance signals for the 2-H protons of cBisNAH(C_4,*o*-Xyl) and its dehydrogenated species [cBisNA$^+$(C_4,*o*-Xyl)] are shifted upfield by 0.3 and 0.5 ppm relative to those of (*N*-Et)BNAH and (*N*-Et)BNA$^+$, respectively. The ring-current effects specifically provided on the 2-H protons in the conformationally fixed state become clearer when one compares the NMR spectrum of cBisNAH(C_4,*o*-Xyl) with that of its open-chain analogue [BisNAH(Et,*o*-Xyl)], and a large chemical shift difference is noted

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Table II. Electronic Absorption Maxima[a] and ^{1}H NMR Chemical Shifts[b] for Dihydronicotinamides

dihydronicotinamide	λ_{max}, nm	^{1}H chemical shifts, δ									
		2-H	4-H	5-H	6-H	phenyl H's	CONH	NCH_2	$CONHCH_2$	CH_2[c]	CH_3
BisNAH(C_4,Bzl)	350	7.03	3.10	4.63	5.65	7.19	5.65	4.20	3.28	1.55	
BisNAH(C_6,Bzl)	350	7.06	3.12	4.66	5.70	7.21	5.40	4.22	3.24	1.37	
BisNAH(C_8,Bzl)	350	7.03	3.10	4.65	5.68	7.19	5.40	4.20	3.22	1.30	
BisNAH(C_{10},Bzl)	350	7.04	3.10	4.65	5.68	7.19	5.30	4.22	3.22	1.29	
BisNAH(Et,*p*-Xyl)	348	7.00	3.08	4.63	5.65	7.11	5.40	4.19	3.22		1.11
BisNAH(Et,*m*-Xyl)	348	7.08	3.13	4.70	5.72	7.20	5.16	4.25	3.34		1.14
BisNAH(Et,*o*-Xyl)	348	7.11	3.20	4.79	5.73	7.35	5.42	4.32	3.43		1.17
cBisNAH(C_4,*p*-Xyl)	345	6.38	3.08	4.70	5.93	7.24	5.20	4.20	3.25	1.35	
cBisNAH(C_6,*p*-Xyl)	348	6.70	3.11	4.71	5.92	7.20	5.35	4.16	3.18	1.30	
cBisNAH(C_4,*o*-Xyl)	343	6.72	3.13	4.73	5.75	7.20	6.20	4.27	3.30	1.55	
(*N*-Et)BNAH	348	7.02	3.10	4.62	5.65	7.17	5.65	4.18	3.30		1.10
BisNAH(C_6,Pr)	352	6.90	3.10	4.61	5.66		5.35	3.00	3.24	1.37	0.88
BisNAH(Pr,C_6)	352	6.90	3.10	4.60	5.63		5.25	3.03	3.22	1.35	0.91
cBisNAH(C_6,C_6)	351	6.97	3.18	4.68	5.67		5.67	3.07	3.32	1.4	
(*N*-Pr)PNAH	352	6.89	3.08	4.58	5.62		5.25	2.97	3.20	1.51	0.88
(*N*-Et-I)BNAH	346	*d*	2.88	4.52	5.58	6.8–7.6[e]	5.30	4.10	3.58	2.98	

[a] Measured in CH_2Cl_2. [b] Measured in $CDCl_3$. Chemical shifts are given in ppm downfield from Me_4Si. Multiplicities: 2-H, s; 4-H, m; 5-H, m; 6-H, d; phenyl H's, s (m for BisNAH(Et,*m*-Xyl)); CONH, broad; NCH_2, s for BisNAH(C_n,Bzl), BisNAH(Et,*x*-Xyl), cBisNAH(C_n,*p*-Xyl), cBisNAH(C_4,*o*-Xyl), (*N*-Et)BNAH, and (*N*-Et-I)BNAH and t for the rest; $CONHCH_2$, q; other methylene H's, m (t for (*N*-Et-I)BNAH); CH_3, t. [c] Other methylene protons. [d] Obscured by overlapping resonance of aromatic protons. [e] Overlapped with signals of the indole-ring protons.

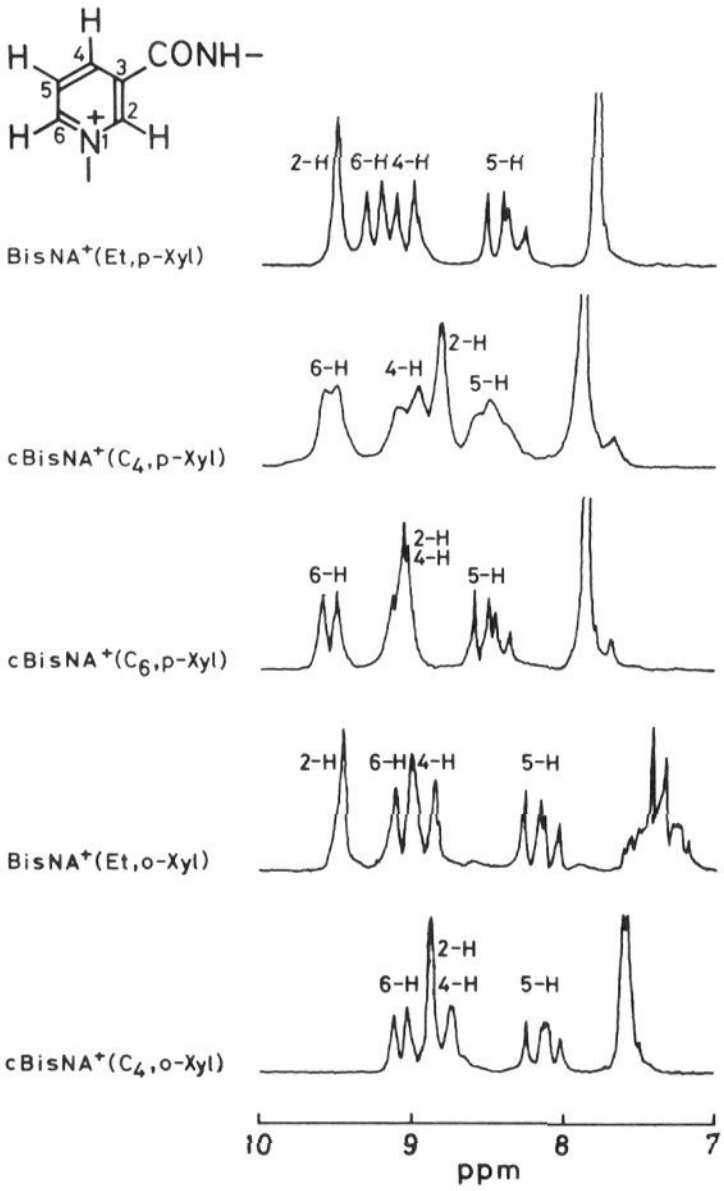
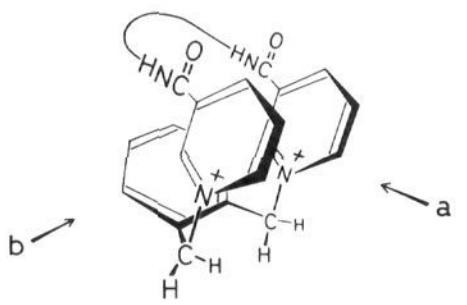


Figure 1. ^{1}H NMR spectra for pyridine ring protons of bis(nicotinamide)s measured in D_2O at room temperature; internal reference DSS.



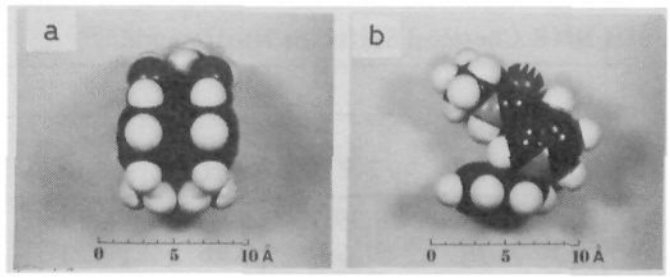


Figure 2. Corey–Pauling–Koltum molecular model of cBisNA$^+$(C_4,*o*-Xyl): (a) view from a direction parallel to the nicotinamide rings; (b) view from a direction perpendicular to the nicotinamide rings.

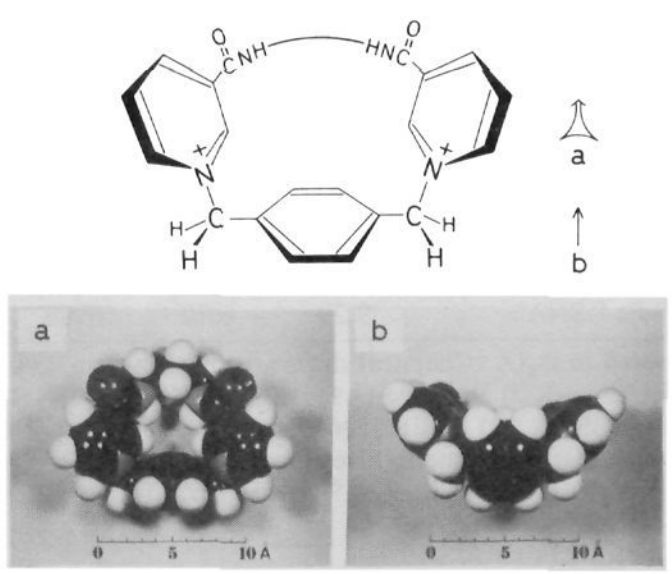
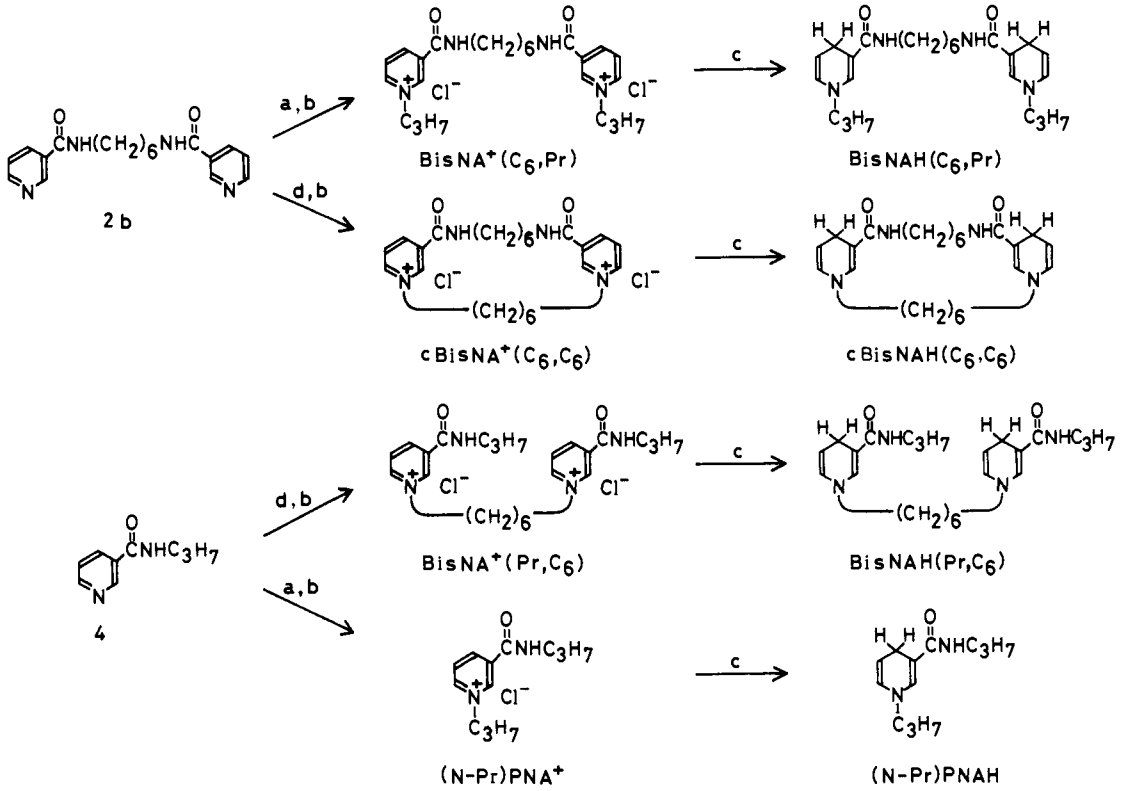


Figure 3. Corey–Pauling–Koltum molecular model of cBisNA$^+$(C_4,*p*-Xyl): (a) top view of the macrocyclic ring; (b) side view of the macrocyclic ring.

only for 2-H protons, BisNAH(Et,*o*-Xyl) having normal 2-H resonance. The same is true also for cBisNA$^+$(C_4,*o*-Xyl) vs. BisNA$^+$(Et,*o*-Xyl). The CPK molecular models for the *p*-xylylene-bridged cyclic derivatives, cBisNAH(C_n,*p*-Xyl), and their dehydrogenated species [cBisNA$^+$(C_n,*p*-Xyl)] indicate that the two nicotinamide planes are tilted relative to each other from the parallel geometry (Figure 3). The tilted orientation is in such a way that the nicotinamide 2-H protons are placed inward of the benzene ring while the 6-H protons are displaced outside the region. This situation is reflected on the NMR spectra of cBisNAH(C_n,*p*-Xyl) and cBisNA$^+$(C_n,*p*-Xyl) in which ring-current effects provided by the benzene ring are reasonably site sensitive and also manipulated by the chain length (n), upfield shifts for 2-H's and downfield ones for 6-H's relative to the chemical shifts for those protons of (*N*-Et)BNAH and (*N*-Et)BNA$^+$. On the other hand, flexible noncyclic bis(1,4-dihydronicotinamides), BisNAH(C_n,Bzl), BisNAH(Et,*p*-Xyl), and BisNAH(Et,*m*-Xyl), and their dehydrogenated counterparts showed normal NMR spectra due to their extended structures, the chemical shifts for

Scheme II[a]



[a] Reagents: a, C_3H_7I; b, ion exchange; c, $Na_2S_2O_4$; d, $I(CH_2)_6I$.

Table III. ^1H NMR Chemical Shifts for Nicotinamides[a]

	chemical shifts, δ								
nicotinamide	2-H	4-H	5-H	6-H	phenyl H's	N^+CH_2	$CONHCH_2$	other methylene H's	CH_3
BisNA$^+$(C_4,Bzl)	9.39	8.96	8.29	9.18	7.56	6.00	3.60	1.88	
BisNA$^+$(C_6,Bzl)	9.39	8.96	8.30	9.19	7.58	6.02	3.57	1.63	
BisNA$^+$(C_8,Bzl)	9.50	9.05	8.40	9.32	7.62	6.11	3.55	1.44	
BisNA$^+$(C_{10},Bzl)	9.53	9.10	8.42	9.39	7.59	6.12	3.52	1.29	
BisNA$^+$(Et,*p*-Xyl)	9.50	9.05	8.37	9.26	7.78	6.14	3.58		1.40
BisNA$^+$(Et,*m*-Xyl)	9.36	8.93	8.23	9.12	7.66	6.02	3.54		1.32
BisNA$^+$(Et,*o*-Xyl)	9.46	8.90	8.13	9.05	7.36	6.25	3.36		1.22
cBisNA$^+$(C_4,*p*-Xyl)	8.82	9.05	8.50	9.53	7.88	6.21	3.5	1.75	
cBisNA$^+$(C_6,*p*-Xyl)	9.05	9.05	8.47	9.54	7.84	6.17	3.58	1.58	
cBisNA$^+$(C_4,*o*-Xyl)	8.88	8.80	8.12	9.07	7.60	6.17	3.40	1.75	
(*N*-Et)BNA$^+$	9.42	8.98	8.31	9.21	7.56	6.01	3.57		1.40
BisNA$^+$(C_6,Pr)	9.21	8.82	8.15	8.98		4.69	3.47	2.12,[b] 1.55[c]	1.03
BisNA$^+$(Pr,C_6)	9.18	8.80	8.12	8.95		4.69	3.39	2.05,[d] 1.50[e,f]	0.98
cBisNA$^+$(C_6,C_6)	9.24	8.80	8.15	8.98		4.72	3.48	2.15,[d] 1.55[c,f]	
(*N*-Pr)PNA$^+$	9.19	8.80	8.12	8.96		4.66	3.39	2.11,[b] 1.68[e]	1.01,[g] 0.98[h]
(*N*-Et-I)BNA$^+$	9.29	8.70	7.88	8.90	7.36	5.72	3.65	3.01 (6.8-7.5)[i]	

[a] Measured in D_2O. Chemical shifts are given in ppm downfield from DSS. Multiplicities: 2-H, s; 4-H, d; 5-H, m; 6-H, d; phenyl H's, s (m for BisNA$^+$(Et,*o*-Xyl) and broad s for cBisNA$^+$(C_4,*o*-Xyl)); N^+CH_2, s for BisNA$^+$(C_n,Bzl), BisNA$^+$(Et,*x*-Xyl), cBisNA$^+$(C_n,*p*-Xyl), cBisNA$^+$(C_4,*o*-Xyl), (*N*-Et)BNA$^+$, and (*N*-Et-I)BNA$^+$ and t for the rest; $CONHCH_2$, q for BisNA$^+$(Et,*x*-Xyl), m for cBisNA$^+$(C_n,*p*-Xyl), cBisNA$^+$(C_4,*o*-Xyl), and t for the rest; other methylene H's, m (t for (*N*-Et-I)BNA$^+$); CH_3, t. [b] $N^+CH_2CH_2CH_2CH_3$. [c] $NHCH_2(CH_2)_4CH_2NH$. [d] $N^+CH_2CH_2(CH_2)_2CH_2CH_2N^+$. [e] $NHCH_2CH_2CH_3$. [f] $N^+CH_2CH_2(CH_2)_2CH_2CH_2N^+$. [g] $N^+CH_2CH_2CH_2CH_3$. [h] $NHCH_2CH_2CH_2CH_3$. [i] indolyl H's (m).

respectively protons being almost identical with those for the corresponding protons of (*N*-Et)BNAH and (*N*-Et)BNA$^+$.

The hexamethylene-bridged face-to-face dimer [cBisNAH(C_6,C_6)] shows all its dihydronicotinamide proton signals slightly shifted downfield relative to those for its monomeric analogue [(*N*-Pr)PNAH] and singly linked counterparts [BisNAH(C_6,Pr) and BisNAH(Pr,C_6)]. The shifts observed for cBisNAH(C_6,C_6) seem to result from the magnetic field effect on the dihydronicotinamide moiety provided by the accompanying dihydronicotinamide ring placed in a close proximity within the same molecule, even though such a field effect is not obvious for its NA$^+$–NA$^+$ counterpart. The CPK molecular model for cBisNAH(C_6,C_6) indicates the following points: (a) the molecule is conformationally more flexible than cBisNAH(C_n,*p*-Xyl) and cBisNAH(C_4,*o*-Xyl); (b) the intramolecular rotational freedom allows a significant deviation of the two nicotinamide rings from a face-to-face conformation.

1,4-Dihydronicotinamides generally show a characteristic absorption at around 350 nm. The absorption maxima for the present bis(dihydronicotinamides) are listed in Table II. Most of the bis(dihydronicotinamides) exhibit their absorption maxima in the same region as those for (*N*-Et)BNAH and (*N*-Pr)PNAH,[17] with

one notable exception of cBisNAH(C_4,*o*-Xyl). The apparent blue shift for cBisNAH(C_4,*o*-Xyl) must be taken as evidence for the electronic interaction between two dihydronicotinamide moieties in enforced proximity.[18]

Reduction of Hexachloroacetone: Intramolecular Electronic Interaction of Kinetic Significance. The kinetic behavior of BisNAH(C_6,Bzl) in the reduction of a carbonyl substrate is given in detail here to represent the novel feature of bis(dihydronicotinamide) reactivity. The reduction of hexachloroacetone[19] (6–10-fold molar excess) with BisNAH(C_6,Bzl) took place readily in dichloromethane or deuteriochloroform and gave the oxidized bis(nicotinamide) salt [BisNA$^+$(C_6,Bzl)] as identified by ^{1}H NMR and HPLC, and 1,1,1,3,3,3-hexachloro-2-propanol in 100% yield, based on the amount of BisNAH(C_6,Bzl) used, as confirmed by GLC (for CH_2Cl_2 solution) and ^{1}H NMR analysis (for $CDCl_3$ solution). When the substrate was used in a large excess [BisNAH(C_6,Bzl), 5.0×10^{-5} M; $(Cl_3C)_2CO$, 1.0×10^{-2} M; in CH_2Cl_2 at 25.0 ± 0.1 °C], the rate of disappearance of the characteristic absorption observed for BisNAH(C_6,Bzl) at 350 nm was much greater (half-life $t_{1/2}$ 40 s) than that for (*N*-Et)BNAH ($t_{1/2}$ 1.2 $\times 10^3$ s). When the reaction medium was deoxygenated prior to the initiation of reaction, the initial rapid loss of the absorbance intensity up to about 50% conversion of BisNAH(C_6,Bzl), as a result of the reaction of the bis(dihydronicotinamide) with the added substrate, was followed by much slower decay. On the other hand, the reaction behavior of (*N*-Et)BNAH remained practically the same regardless of conditions, aerobic or anaerobic. The solvent effect on the reactivity of BisNAH(C_6,Bzl) is also noteworthy: a change of solvent from dichloromethane to a more polar one, acetonitrile, resulted in a 3-fold increase in $t_{1/2}$. This is in marked contrast to the solvent effect on the reactivity of (*N*-Et)BNAH, 10 times more reactive in acetonitrile than in dichloromethane. Thus, the acceleration factors, in terms of $t_{1/2}$, for BisNAH(C_6,Bzl) vz. (*N*-Et)BNAH is 1.1:1 in CH_3CN, 30:1 in CH_2Cl_2, and even greater (46:1) in a more apolar solvent, $CHCl_3$. The solvent polarity parameters, $E_T(30)$, are 46.0, 41.1, and 39.1 for CH_3CN, CH_2Cl_2, and $CHCl_3$, respectively.[20] The observed solvent effect in the reduction with (*N*-Et)BNAH can be understood in terms of the transition-state character: the transition state becomes more polar than the initial state and can be stabilized in a more polar microenvironment consequently. An anomalous solvent effect in the reduction with BisNAH(C_6,Bzl) clearly suggests that another interaction mode takes place within the molecule in the transition state. Such an interaction must be favored in less polar solvents, so that the charge-delocalized transition state becomes stabilized.

The reaction of a nondegassed, equimolar mixture of BisNAH(C_6,Bzl) and hexachloroacetone in deuteriochloroform (i.e., ketone:dihydronicotinamide unit = 0.5:1) yielded NA$^+$–NA$^+$ species quantitatively (confirmed by ^{1}H NMR spectroscopy); i.e., one dihydronicotinamide unit in BisNAH(C_6,Bzl) undergoes oxidation without participation of the ketone. This is consistent with the kinetic results under aerobic and anaerobic conditions described above. In contrast, (*N*-Et)BNAH reacted with the ketone on a 1:1 molar basis. In fact, (*N*-Et)BNAH in deuteriochloroform was titrated with hexachloroacetone by NMR techniques. Upon addition of the ketone (0.5 molar equiv) to (*N*-Et)BNAH, exactly half the dihydronicotinamide initially present underwent oxidation, and further addition of the ketone (0.5 equiv) completed the oxidation of the remaining (*N*-Et)-BNAH. In each reaction of BisNAH(C_6,Bzl) and (*N*-Et)BNAH with the substrate, formation of the alcohol product was nearly quantitative, as confirmed by NMR spectroscopy.

Scheme III

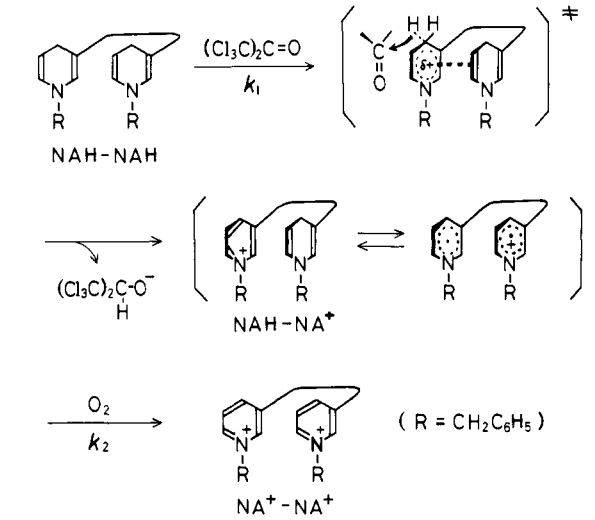


Table IV. Reactivities[a] of Dihydronicotinamides in the Reduction of Hexachloroacetone[b] at 25.0 ± 0.1 °C

dihydronicotinamide	10^3k, s^{-1} in CH_3CN	10^3k, s^{-1} in CH_2Cl_2	k_{rel}[c] (1)	(2)	(3)
BisNAH(C_4,Bzl)	5.7	11	17		
BisNAH(C_6,Bzl)	5.9	11	17		
BisNAH(C_8,Bzl)	6.2	4.8	7.3		
BisNAH(C_{10},Bzl)		3.1	4.7		
BisNAH(Et,*p*-Xyl)	5.9	0.69	1.0		
BisNAH(Et,*m*-Xyl)		4.6	7.0		
BisNAH(Et,*o*-Xyl)		8.6	13		
cBisNAH(C_4,*p*-Xyl)	6.1	4.9	7.4		
cBisNAH(C_6,*p*-Xyl)		3.3	5.0		
cBisNAH(C_4,*o*-Xyl)	5.9	15	23		
(*N*-Et)BNAH	5.7	0.66	*d*		
(*N*-Et-I)BNAH	5.6	7.2	11		
BisNAH(C_6,Pr)		18		9.0	
BisNAH(Pr,C_6)		9.4		4.7	
cBisNAH(C_6,C_6)		9.2		4.6	
(*N*-Pr)PNAH		2.0		*d*	
PNAH	8.2	0.54			*d*
NAH-C_6-Ad	8.1	0.51			0.9

[a] Given in pseudo-first-order rate constants at the initial stage of reaction as evaluated from absorbance change at 350 nm due to disappearance of dihydronicotinamide. [b] Concentrations: NAH unit, 1.0×10^{-4} M; $(Cl_3C)_2CO$, 1.0×10^{-2} M. [c] Relative rate with respect to a selected reference (in CH_2Cl_2). [d] Reference ($k_{rel} = 1.0$).

These results allow to propose the reaction mechanism in such solvents as dichloromethane and chloroform under aerobic conditions (Scheme III). The initial reaction (rate constant k_1) is associated with the reduction of the substrate without participation of dioxygen, and the resulting intermediate (NAH-NA$^+$) undergoes a facile oxidation with dioxygen (rate constant k_2).[21] The k_2 step seems to be reasonable since a protonated pyridinyl radical (NAH$^{+\cdot}$), produced by electrochemical one-electron oxidation of dihydronicotinamides, undergoes ready oxidation with dioxygen to afford NA$^+$ species.[22] The significant acceleration of the k_1 process, the facile oxidation of NAH–NA$^+$, and the specific solvent effect thereupon as well can be understood in a unified manner by postulating an intramolecular electronic interaction of charge-transfer (CT) character in NAH–NA$^+$ and *in the transition state of its formation* (Scheme III). The intermolecular charge-transfer interaction between reduced (NAH) and oxidated

(17) A fluorescence maximum for BisNAH(C_6,Bzl) was observed at 424 nm with excitation at 346 nm in dichloromethane, in the same region as observed for (*N*-Et)BNAH (423 nm).

(18) The fluorescence maximum for cBisNAH(C_4,*o*-Xyl) (435 nm, excitation at 360 nm) in dichloromethane showed a red shift by 12 nm with reference to that for (*N*-Et)BNAH.

(19) For the reduction of hexachloroacetone with simple 1,4-dihydronicotinamides in acetonitrile, see: Dittmer, D. C.; Lombardo, A.; Batzold, F.; Greene, C. S. *J. Org. Chem.* **1976**, *41*, 2976–2981.

(20) Reichardt, C. "Solvent Effects in Organic Chemistry"; Verlag Chemie: Weinheim, 1979; pp 270–272.

(21) In the absence of the ketone, BisNAH(C_6,Bzl) was stable even under aerobic conditions.

(22) Blaedel, W. J.; Haas, R. G. *Anal. Chem.* **1970**, *42*, 918–927.

(NA^+) nicotinamides[23-25] and an electron transfer between them in the course of transhydrogenation, giving a radical cation–radical intermediate,[26] have been demonstrated. Apparently higher concentrations of NAH and NA^+ species are required for such intermolecular processes.

In the light of the kinetically significant CT interaction shown in Scheme III, one of the two dihydronicotinamides (NAH) is expected to be replaceable by other potential donors, e.g., indoles,[25,27] capable of CT interaction with NA^+. A molecule having an indole moiety in addition to a dihydronicotinamide group is typical of this situation, and (*N*-Et-I)BNAH was found to be more than 10 times as reactive as (*N*-Et)BNAH in dichloromethane (Table IV). The oxidation product, (*N*-Et-I)BNA^+, showed a long absorption tail extended to the 450-nm range, which may be attributed to the intramolecular CT transition. The oxidized pyridine coenzymes (NAD^+ and $NADP^+$) or their model compound, 1-benzyl-3-carbamoylpyridinium chloride, undergo similar CT interaction with tryptophan and other indole derivatives, as confirmed by electronic spectroscopy.[27] Such a CT interaction was further shown by fluorescence spectroscopy applied on a model compound, 3-[*N*-(β-(3-indolyl)ethyl)carbamoyl]pyridinium chloride.[28] Our present findings point out the possibility of kinetic enhancement through CT interactions of the NAD(P)H moiety with some potential donors in biological systems.

In contrast, poor electron donors cannot enhance the reactivity of dihydronicotinamide by the intramolecular electronic interaction. The reactivity of an NADH analogue having an adenyl moiety (NAH-C_6-Ad) was almost identical with that of PNAH. This reflects the poor electron-donating ability of adenine compared with dihydronicotinamide and indole moieties.

Whenever bis(1,4-dihydronicotinamides) of the present study exhibited reactivity significantly greater than the monodihydronicotinamide [(*N*-Et)BNAH], the reduction must proceed through the same steps as shown in Scheme III on the basis of their kinetic behavior under aerobic conditions.

Reactivity of Bis(1,4-dihydronicotinamides): Geometrical Requirement for Electronic Interaction. The reactivity data for the bis(1,4-dihydronicotinamides) in acetonitrile and dichloromethane are summarized in Table IV. The reactivity is given in terms of a pseudo-first-order rate constant evaluated from the rate of disappearance of bis(dihydronicotinamide) at the initial stage of reaction in the presence of excess ketone (1.0×10^{-2} M) under aerobic conditions.[29] The reactivities of some reductants [BisNAH(C_n,Bzl) for n = 4, 6, and 8, BisNAH(Et,*p*-Xyl), cBisNAH(C_4,*p*-Xyl), and cBisNAH(C_4,*o*-Xyl)] are in a range of $(5.7–6.2) \times 10^{-3}$ s^{-1} in acetonitrile and comparable to that of (*N*-Et)BNAH. This implies that the intramolecular electronic interaction between the two nicotinamide moieties cannot be kinetically effective in such a polar solvent that may stabilize a charge-isolated state more favorably than a charge-delocalized one, shown in Scheme III. On the other hand, a wide variety of reactivity was observed in dichloromethane. Among the bis(dihydronicotinamides) regarded as dimers of (*N*-Et)BNAH, cBisNAH(C_4,*o*-Xyl) was found to be the most reactive. This is consistent with a view that a close face-to-face conformation for the two nicotinamide rings is the primary requirement for an electronic interaction of kinetic significance (Figure 2). The *p*-xylylene-bridged cyclic species, cBisNAH(C_n,*p*-Xyl) with n = 4 and 6, are 3.1 and 4.6 times less reactive than cBisNAH-(C_4,*o*-Xyl), respectively. The unfavorable reactivity is attributed to some deviation of geometry from an ideal, close face-to-face arrangement of two dihydronicotinamides: an increased intramolecular distance and a tilted mutual orientation of the two nicotinamide planes (Figure 3).

As regards the noncyclic bis(dihydronicotinamides), variation of reactivity associated with *o*-, *m*-, and *p*-xylylene linkage isomers [BisNAH(Et,*x*-Xyl), x = *o*-, *m*-, and *p*-, respectively] clearly indicates that the intramolecular separation and relative orientation of two nicotinamides are the governing factors for an effective electronic interaction. BisNAH(Et,*p*-Xyl) is nothing more than a simple, functionally identical analogue of (*N*-Et)BNAH on the basis of reactivity criterion and kinetic solvent and oxygen effects. In addition to the fact that the two nicotinamide moieties in BisNAH(Et,*p*-Xyl) are separated by a *p*-xylylene bridge, they may take various orientations relative to each other due to rotation about C(aromatic)–CH_2 and CH_2–N bonds and become electronically independent of each other. Another class of noncyclic bis(dihydronicotinamides) [BisNAH(C_n,Bzl)] shows an interesting reactivity pattern. In contrast to the rigid *p*-xylylene bridge, the flexible polymethylene chain in BisNAH(C_n,Bzl) may allow a close face-to-face conformation to be assumed in the transition state of reduction as well as in the ground state (in a statistical sense) if n = 4 or 6. The extent of electronic interaction between the nicotinamide moieties is also subjected to change sensitively by the chain length (n); an increment by only two CH_2's resulted in a large reduction in reactivity (from n = 6 to 8).

Comparison of reactivities among noncyclic and cyclic bis(dihydronicotinamides) further allows characterization of the intrinsic electronic interaction. The *p*-xylylene-bridged cyclic ones [cBisNAH(C_n,*p*-Xyl)] are several times more reactive than the corresponding noncyclic counterpart [BisNAH(Et,*p*-Xyl)]. This reflects the electronic effect provided by fixation of relative orientation of the two nicotinamides. Meanwhile, cBisNAH(C_n,*p*-Xyl) shows reduced reactivity as compared with another noncyclic family [BisNAH(C_n,Bzl)]. The overall reactivity order is as follows: BisNAH(C_n,Bzl) (n = 4, 6) > cBisNAH(C_n,*p*-Xyl) (n = 4, 6) > BisNAH(Et,*p*-Xyl) = (*N*-Et)BNAH. An important view emerges from this correlation as to the consequence of conformational fixation and flexibility in the ground state. cBisNAH(C_n,*p*-Xyl) is conformationally fixed but rather in a wrong way with respect to both internal distance and angle between the nicotinamide rings. On the other hand, the two nicotinamides in BisNAH(C_n,Bzl) (particularly with n = 4 and 6) may be allowed to take a close face-to-face geometry without inducing significant strain in the transition state of reduction, even though it may take an extended molecular geometry in the ground state with minimum electronic interaction judging from its normal spectroscopic properties (^{1}H NMR, electronic, and fluorescence[17] measurements). In brief, the effective CT interaction, which gives out kinetic enhancement, emerges from the favorable face-to-face arrangement of the two dihydronicotinamide moieties in the transition state. Such arrangement is apparently subjected to change by the nature of bridging components that link two nicotinamide moieties. As regards the nature of bridging components, a flexible single bridge [BisNAH(C_n,Bzl)] can provide a better kinetic effect than an unfavorably fixing double bridge [cBisNAH(C_n,*p*-Xyl)], which in turn is better than a less flexible single bridge [BisNAH(Et,*p*-Xyl)]. The conformational fixation in fact results in reactivity enhancement with an *o*-xylylene bridge, even if it is used as a single-bridge component. A favorably fixing double bridge [cBisNAH(C_4,*o*-Xyl)] is better than both of the single-bridge types.

The reactivity of bis(dihydronicotinamides) regarded as dimers of (*N*-Pr)PNAH are also subject to change by the nature of bridging components and follows the sequence BisNAH(C_6,Pr) > cBisNAH(C_6,C_6) ≃ BisNAH(Pr, C_6) > (*N*-Pr)PNAH. Nearly identical reactivities for cBisNAH(C_6,C_6) and BisNAH(Pr,C_6) may require some comments. Even though BisNAH(Pr,C_6) is structurally comparable to BisNAH(Et,*p*-Xyl), the former gives out an enhanced reactivity relative to the latter owing to its flexible alkyl-chain bridge in place of a *p*-xylylene moiety

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(28) Shifrin, S. *Biochim. Biophys. Acta* **1964**, *81*, 205–213.
(29) The kinetic behavior of BisNAH(C_6,Bzl), cBisNAH(C_6,*p*-Xyl), and cBisNAH(C_4,*o*-Xyl) was carefully examined in dichloromethane under both aerobic and anaerobic conditions. Rate constants for the k_1 process under anaerobic conditions, where the k_2 process is lacking, are practically identical with those obtained under aerobic conditions. This result also indicates that $k_2 \gg k_1$ for aerobic runs with these bis(dihydronicotinamides).

involved in the latter and also a greater reactivity than (*N*-Pr)-PNAH due to the same reason given for BisNAH(C_n,Bzl). Two dihydronicotinamide moieties are linked doubly with flexible alkyl chains in cBisNAH(C_6,C_6), but are far from the face-to-face geometry even if they are forced to approach to such conformation. Thus, it is less reactive than cBisNAH(C_4,*o*-Xyl) due to limited CT interaction in the transition state of reduction.

Conclusion

The extensive intramolecular nicotinamide–nicotinamide electronic interaction gives out large kinetic effects in the reduction of hexachloroacetone. The interaction needs to be provided in the transition state rather than in the ground state and is of charge-transfer character between the two dihydronicotinamide moieties placed in a close face-to-face conformation. The face-to-face geometry must be attained without inducing internal steric strain, regardless of the nature of bridging components that link two dihydronicotinamide moieties. When the dihydronicotinamide groups are rigidly fixed in such a favorable geometry already in the ground state, however, the kinetic effect becomes most pronounced by the entropy effect. In the present reaction, one of the dihydronicotinamide groups serves as an electron pool. Consequently, such an electron pool can be replaced with other potential electron-donating moieties.

The chemistry of 1-alkyl-1,4-dihydronicotinamides, as coenzyme NAD(P)H models, has been a subject of considerable interest in these years. Much attention has been focused on the *activation of substrates* via metal ion coordination,[30-34] hydrogen bonding,[35,36] and general acid catalysis.[37,38] On the other hand, we have shown here a direction for designing 1-alkyl-1,4-dihydronicotinamide, so that the reductant undergoes *self-activation via CT electronic interaction*[39] in the transition state. The structure–reactivity correlation established in the present work provides a basis for the development of more elaborated, multicenter organic redox catalysts.

Experimental Section

General Analyses and Measurements. Elemental analyses were performed at the Microanalysis Center of Kyushu University. Melting points were measured with capillary tubes with a Yamato MP-1 melting point apparatus (oil bath type). Infrared spectra were recorded on a JASCO IR-E spectrophotometer. ^{1}H NMR spectra were taken on a Hitachi R-20, a Bruker WH-90 FT, or a JEOL FX-100 spectrometer. Fluorescence and electronic absorption spectra were obtained with a Hitachi 650-60 spectrofluorometer and a Union Giken SM-401 high sensitivity spectrophotometer, respectively. High-performance liquid chromatography (HPLC) for preparative purposes was carried out on a Hitachi 635 liquid chromatograph with Hitachi gel 3019. Gel filtration chromatography was performed on a column packed with Sephadex LH-20 or Toyopearl HW-40 fine. Methanol was used as eluant for both chromatographic methods unless otherwise indicated, and components eluted were detected by UV absorption at either 254 or 265 nm for both chromatographic methods. Gas chromatographic analyses were made with a Shimadzu GC-4C gas chromatograph on a 2-m column packed with 10% silicone DC-550 with helium as a carrier gas. Molecular weight measurements were carried out with a Hitachi Perkin-Elmer 115 vapor pressure osmometer for identification of macrocyclic compounds.

DMF as a solvent for preparative purposes was distilled in vacuo over BaO and stored under nitrogen. Dichloromethane for kinetic studies was fractionally distilled and stored over 4-Å molecular sieves. Acetonitrile was purified according to the method of literature.[31] Hexachloroacetone was distilled just before use (bp 110 °C (40 mmHg)).

***N*,*N*′-Alkylenebis(3-carbamoylpyridines) (2).** To a solution of nicotinoyl chloride (**1**) (11.5 g, 80 mmol) in benzene (30 mL) was added a benzene solution (50 mL) of an appropriate α,ω-diaminoalkane (34 mmol) and pyridine (15 g, 190 mmol). The mixture was stirred at room temperature for 1 day and evaporated in vacuo. Water (100 mL) was added and the mixture stirred for 2 h. Precipitates were recovered by filtration, washed with 10% aqueous NaOH and water, and recrystallized from methanol.

***N*,*N*′-Alkylenebis(1-benzyl-3-carbamoylpyridinium) Dichlorides, BisNA$^+$(C_n,Bzl).** A mixture of benzyl chloride (2 g, 16 mmol) and an appropriate *N*,*N*′-alkylenebis(3-carbamoylpyridine) (**2**) (1.5 mmol) in DMF (5 mL) was stirred under nitrogen at 120–130 °C for 10 h. After the mixture was cooled, volatile materials were removed in vacuo and the residue was dissolved in water (20 mL). Insoluble materials were removed by filtration, and the filtrate was washed with ether (3 × 20 mL) and evaporated to give a crude product. This was purified by either gel filtration chromatography with Sephadex LH-20 [for BisNA$^+$(C_n,Bzl); n = 4, 8, and 10] or recrystallization from methanol–ether.

(a) BisNA$^+$(C_4,Bzl): a very hygroscopic white solid, yield 770 mg (93%). Anal. Calcd for $C_{30}H_{32}Cl_2N_4O_2\cdot H_2O$: C, 63.27; H, 6.02; N, 9.84. Found: C, 63.61; H, 6.09; N, 9.90.

(b) BisNA$^+$(C_6,Bzl): white needles, yield 630 mg (73%), mp 133.5–135.5 °C dec. Anal. Calcd for $C_{32}H_{36}Cl_2N_4O_2\cdot H_2O$: C, 64.32; H, 6.41; N, 9.38. Found: C, 64.69; H, 6.53; N, 9.22.

(c) BisNA$^+$(C_8,Bzl): a pale brown oil, yield 860 mg (94%). Anal. Calcd for $C_{34}H_{40}Cl_2N_4O_2\cdot 0.5H_2O$: C, 66.23; H, 6.70; N, 9.09. Found: C, 66.14; H, 6.76; N, 9.03.

(d) BisNA$^+$(C_{10},Bzl): a pale brown oil, yield 800 mg (84%). Anal. Calcd for $C_{36}H_{44}Cl_2N_4O_2\cdot 0.5H_2O$: C, 67.07; H, 7.04; N, 8.69. Found: C, 66.94; H, 7.14; N, 8.54.

1,1′-Xylylenebis[3-(*N*-ethylcarbamoyl)pyridinium] Dihalides, BisNA$^+$(Et,*x*-Xyl). These were prepared from *N*-ethylnicotinamide (**3**) (1.5 g, 10 mmol) and a xylylene dihalide (5 mmol) in a manner similar to that for the preparation of BisNA$^+$(C_n,Bzl).

(a) BisNA$^+$(Et,*p*-Xyl): white needles recrystallized from methanol–ether, yield 2.25 g (95%), mp 224.0–224.5 °C dec. Anal. Calcd for $C_{24}H_{28}Cl_2N_4O_2\cdot 0.33H_2O$: C, 59.88; H, 6.00; N, 11.64. Found: C, 60.04; H, 5.94; N, 11.34.

(b) BisNA$^+$(Et,*m*-Xyl): white needles recrystallized from methanol, yield 2.0 g (71%), mp 134–136 °C. Anal. Calcd for $C_{24}H_{28}Br_2N_4O_2\cdot 1.5H_2O$: C, 48.75; H, 5.28; N, 9.47. Found: C, 49.04; H, 5.16; N, 9.40.

(c) BisNA$^+$(Et,*o*-Xyl): a glassy material purified by gel filtration chromatography (Sephadex LH-20), yield 0.71 g (25%). Anal. Calcd for $C_{24}H_{28}Br_2N_4O_2\cdot 0.5H_2O$: C, 50.29; H, 5.10; N, 9.77. Found: C, 50.60; H, 5.06 N, 9.48.

1,8-Dioxo-2,7,13,23-tetraaza[8.1.1]metaparametacyclophane Dichloride, cBisNA$^+$(C_4,*p*-Xyl). A solution of **2a** (550 mg, 1.85 mmol) in DMF (100 mL) and a solution of *p*-xylylene dichloride (500 mg, 2.86 mmol) in DMF (100 mL) were added dropwise to DMF (600 mL) at the same rate with vigorous stirring under nitrogen in a period of 8 h at 125 °C, and the mixture was stirred for an additional 1 h at the same temperature. The solvent was removed in vacuo, and the residue was dissolved in water (30 mL). Insoluble materials were removed by filtration, and the filtrate was washed with ether (4 × 20 mL). The solvent was removed in vacuo, and the residue was purified by gel filtration chromatography (Sephadex LH-20 and Toyopearl HW-40 fine) to afford a glassy material; yield 77 mg (9%), a single peak by HPLC analysis. A molecular weight determined by osmometry in methanol was consistent with formation of the 1:1 adduct. Anal. Calcd for $C_{24}H_{26}Cl_2N_4O_2\cdot 0.67H_2O$: C, 59.39; H, 5.68; N, 11.54. Found: C, 59.21; H, 5.63; N, 11.47.

1,10-Dioxo-2,9,15,25-tetraaza[10.1.1]metaparametacyclophane Dichloride, cBisNA$^+$(C_6,*p*-Xyl). This was prepared from **2b** (4.0 g, 12 mmol) and *p*-xylylene dichloride (2.8 g, 16 mmol) by the same procedure as employed for the synthesis of cBisNA$^+$(C_4,*p*-Xyl). After being isolated by gel filtration chromatography (Sephadex LH-20), the product was recrystallized from methanol to afford a white powder; yield 780 mg (13%), mp 207–209 °C dec, a single peak by HPLC analysis. A molecular weight determined by osmometry in methanol was consistent with formation of the 1:1 adduct. Anal. Calcd for $C_{26}H_{30}Cl_2N_4O_2\cdot 0.5H_2O$: C, 61.18; H, 6.12; N, 10.98. Found: C, 61.00 H, 6.16; N, 10.92.

1,8-Dioxo-2,7,13,23-tetraaza[8.1.1]metaorthometacyclophane Dibromide, cBisNA$^+$(C_4,*o*-Xyl). The reaction was carried out with **2a** (1.0 g, 3.4 mmol) and *o*-xylylene dibromide (1.0 g, 3.8 mmol) in DMF by the same procedure as employed for the preparation of cBisNA$^+$(C_4,*p*-Xyl), and the product was recrystallized from methanol–water to give colorless needles; yield 813 mg (43%), mp 250–251 °C dec, a single peak by gel filtration chromatography (Sephadex G-10, water as eluant). A mo-

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lecular weight determined by osmometry in water was consistent with formation of the 1:1 adduct. Anal. Calcd. for $C_{24}H_{26}Br_2N_4O_2$: C, 51.26; H, 4.66; N, 9.96. Found: C, 50.85; H, 4.72; N, 9.75.

N,N'-Hexamethylenebis(1-propyl-3-carbamoylpyridinium) Dichloride, BisNA$^+$(C_6,Pr). A mixture of **2b** (1.0 g, 3 mmol) and *n*-propyl iodide (2.0 g, 12 mmol) in DMF (5 mL) was stirred at room temperature for 12 days. Volatile materials were removed in vacuo, and the residue dissolved in water (20 mL) was applied on a column (1.5 × 30 cm) of Dowex 1-X8(Cl^-) twice. Further purification by gel filtration chromatography (Toyopearl HW-40 fine) afforded the product as a white powder; yield 1.13 g (77%), mp 192–193 °C. Anal. Calcd for $C_{24}H_{36}Cl_2N_4O_2 \cdot 0.5H_2O$: C, 58.53; H, 7.57; N, 11.38. Found: C, 58.78; H, 7.60; N, 11.76.

1,1'-Hexamethylenebis[3-(N-propylcarbamoyl)pyridinium] Dichloride, BisNA$^+$(Pr,C_6). This was prepared from *N*-propylnicotinamide (**4**) (500 mg, 3 mmol) and 1,6-diiodohexane (500 mg, 1.5 mmol) in reference to the method for the preparation of BisNA$^+$(C_6,Pr); a white powder, yield 656 mg (89%), mp 189 °C. Anal. Calcd for $C_{24}H_{36}Cl_2N_4O_2 \cdot 0.5H_2O$: C, 58.53; H, 7.37; N, 11.38. Found: C, 58.72; H, 7.42; N, 11.30.

1,10-Dioxo-2,9,15,23-tetraaza[10.6]metacyclophane Dichloride, cBisNA$^+$(C_6,C_6). The cyclization–bisquaternization of **2b** (1.0 g, 3.1 mmol) with 1,6-diiodohexane (1.0 g, 3.0 mmol) was carried out in reference to the procedure for the preparation of cBisNA$^+$(C_4,*p*-Xyl). The solvent was removed after the reaction was completed, and the residue dissolved in water (40 mL). A precipitated solid was removed by filtration, and the filtrate was applied on a column (1.5 × 30 cm) of Dowex 1-X8(Cl^-) twice. Further purification by gel filtration chromatography (Sephadex LH-20 and Toyopearl HW-40 fine) afforded the product as a white powder; yield 70 mg (5%), mp 241–242 °C dec, a single peak by HPLC analysis. A molecular weight determined by osmometry in methanol was consistent with formation of the 1:1 adduct. Anal. Calcd for $C_{24}H_{34}Cl_2N_4O_2 \cdot 0.5H_2O$: C, 58.77; H, 7.19; N, 11.42. Found: C, 58.78; H, 7.23; N, 11.37.

1-Benzyl-3-(*N*-ethylcarbamoyl)pyridinium chloride, (*N*-Et)BNA$^+$, and 1-propyl-3-(*N*-propylcarbamoyl)pyridinium chloride, (*N*-Pr)PNA$^+$, were prepared according to the procedure similar to that applied to the synthesis of 1-benzyl-3-carbamoylpyridinium chloride.[40] 1-Benzyl-3-[*N*-(β-(3-indolyl)ethyl)carbamoyl]pyridinium chloride, (*N*-Et-I)BNA$^+$, was prepared in reference to the method for the synthesis of 1-methyl-3-[*N*-(β-(3-indolyl)ethyl)carbamoyl]pyridinium chloride.[19] All the products were identified by elemental analyses and ^{1}H NMR spectroscopy. (*N*-Et)BNA$^+$: white granular crystals recrystallized from ethanol–ether, mp 169–171 °C dec. (*N*-Pr)PNA$^+$: colorless needles purified by gel filtration chromatography (Sephadex LH-20), mp 122–124 °C. (*N*-Et-I)BNA$^+$: a yellow powder recrystallized from methanol–ether, mp 105–106 °C dec.

1-Propyl-3-carbamoyl-1,4-dihydropyridine, PNAH,[41] and 1-[6-(9-adenyl)hexyl]-3-carbamoyl-1,4-dihydropyridine, NAH-C_6-Ad,[42] were prepared according to the published procedures.

Preparation of 1,4-Dihydronicotinamides. An aqueous solution of sodium dithionite (270 mg, 1.5 mmol) in 75 mM sodium carbonate (20 mL) on an ice bath was protected from room light and maintained under nitrogen atmosphere. Upon addition of an aqueous solution (3 mL) of a pyridinium salt (100 mg) in one portion, the mixture immediately turned yellow and became turbid. After the mixture was stirred for 30 min, dichloromethane (20 mL) was added to it and stirring was continued. The reaction was monitored by measuring absorbance of an aliquot sample taken at appropriate time intervals. Absorbance due to the dihydronicotinamide moiety reached a maximum after time elapse of ca. 5 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layer and the extract were combined, washed with water (3 × 30 mL), dried (Na_2SO_4) overnight in a refrigerator, and evaporated in vacuo. The residue was purified by gel filtration chromatography (Sephadex LH-20, absolute methanol as eluant) to afford the product. 1,4-Dihydronicotinamides thus obtained contained a trace amount of methanol, introduced during the course of gel filtration chromatography, as detected by NMR spectroscopy in $CDCl_3$. The present 1,4-dihydronicotinamides were, not unexpectedly, unstable to heat and decomposed gradually even at room temperature. Hence, the compounds were stored under nitrogen in a desiccator, which was placed in a refrigerator. Stock solutions for kinetic runs were prepared immediately before use.

(a) N,N'-Tetramethylenebis(1-benzyl-3-carbamoyl-1,4-dihydropyridine), BisNAH(C_4,Bzl): yellow needles, yield 48 mg (60%). Anal. Calcd for $C_{30}H_{34}N_4O_2 \cdot CH_3OH$: C, 72.35; H, 7.44; N, 10.89. Found: C, 72.59; H, 7.21; N, 11.24.

(b) N,N'-Hexamethylenebis(1-benzyl-3-carbamoyl-1,4-dihydropyridine), BisNAH(C_6,Bzl): a yellow oil, yield 60 mg (68%), fluorescence maximum (CH_2Cl_2) 424 nm (excitation at 346 nm). Anal. Calcd for $C_{32}H_{38}N_4O_2 \cdot CH_3OH$: C, 73.03; H, 7.80; N, 10.32. Found: C, 73.39; H, 7.63; N, 10.46.

(c) N,N'-Octamethylenebis(1-benzyl-3-carbamoyl-1,4-dihydropyridine), BisNAH(C_8,Bzl): a yellow oil, yield 50 mg (56%). Anal. Calcd for $C_{34}H_{42}N_4O_2 \cdot CH_3OH$: C, 73.66; H, 8.12; N, 9.82. Found: C, 73.38; H, 7.89; N, 10.11.

(d) N,N'-Decamethylenebis(1-benzyl-3-carbamoyl-1,4-dihydropyridine), BisNAH(C_{10},Bzl): a yellow oil, yield 23 mg (26%). Anal. Calcd for $C_{36}H_{46}N_4O_2 \cdot CH_3OH$: C, 74.21; H, 8.42; N, 9.36. Found: C, 73.94; H, 8.06; N, 9.21.

(e) 1,1'-p-Xylylenebis[3-(N-ethylcarbamoyl)-1,4-dihydropyridine], BisNAH(Et,*p*-Xyl): a yellow solid, yield 60 mg (70%). Anal. Calcd for $C_{24}H_{30}N_4O_2 \cdot 1.33CH_3OH$: C, 67.73; H, 7.93; N, 12.47. Found: C, 67.60; H, 7.77; N, 12.62.

(f) 1,1'-m-Xylylenebis[3-(N-ethylcarbamoyl)-1,4-dihydropyridine], BisNAH(Et,*m*-Xyl): a yellow solid, yield 30 mg (42%). Anal. Calcd for $C_{24}H_{30}N_4O_2 \cdot 2CH_3OH$: C, 66.37; H, 8.14; N, 11.91. Found: C, 66.12; H, 7.67; N, 12.46.

(g) 1,1'-o-Xylylenebis[3-(N-ethylcarbamoyl)-1,4-dihydropyridine], BisNAH(Et,*o*-Xyl): a yellow solid, yield 47 mg (65%). Anal. Calcd for $C_{24}H_{30}N_4O_2 \cdot 1.33CH_3OH$: C, 67.73; H, 7.93; N, 12.47. Found: C, 67.48; H, 7.56; N, 12.49.

(h) 1,8-Dioxo-2,7,13,23-tetraaza-10,13,23,26-tetrahydro[8.1.1]metaparametacyclophane, cBisNAH(C_4,*p*-Xyl): yellow needles, yield 43 mg (50%). Anal. Calcd for $C_{24}H_{28}N_4O_2 \cdot 1.33CH_3OH$: C, 68.04; H, 7.51; N, 12.53. Found: C, 67.93; H, 7.12; N, 12.98.

(i) 1,10-Dioxo-2,9,15,25-tetraaza-12,15,25,28-tetrahydro[10.1.1]metaparametacyclophane, cBisNAH(C_6,*p*-Xyl): yellow needles, yield 57 mg (67%). Anal. Calcd for $C_{26}H_{32}N_4O_2 \cdot 2CH_3OH$: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.71; H, 7.35; N, 11.21.

(j) 1,8-Dioxo-2,7,13,23-tetraaza-10,13,23,26-tetrahydro[8.1.1]metaorthometacyclophane, cBisNAH(C_4,*o*-Xyl): a yellow solid, yield 2 mg (3%), fluorescence maximum (CH_2Cl_2) 435 nm (excitation at 360 nm). Anal. Calcd for $C_{24}H_{28}N_4O_2 \cdot CH_3OH$: C, 68.78; H, 7.39; N, 12.83. Found: C, 68.23; H, 6.81; N, 12.90.

(k) 1-Benzyl-3-(N-ethylcarbamoyl)-1,4-dihydropyridine, (N-Et)BNAH: a yellow oil, yield 71 mg (81%), fluorescence maximum (CH_2Cl_2) 423 nm (excitation at 346 nm). Anal. Calcd for $C_{15}H_{18}N_2O \cdot 0.33CH_3OH$: C, 72.78; H, 7.70; N, 11.07. Found: C, 72.58; H, 7.41; N, 11.20.

(l) N,N'-Hexamethylenebis(1-propyl-3-carbamoyl-1,4-dihydropyridine), BisNAH(C_6,Pr): a yellow oil, yield 63 mg (74%). Anal. Calcd for $C_{24}H_{38}N_4O_2 \cdot CH_3OH$: C, 67.23; H, 9.48; N, 12.54. Found: C, 67.16; H, 9.07; N, 13.07.

(m) 1,1'-Hexamethylenebis[3-(N-propylcarbamoyl)-1,4-dihydropyridine], BisNAH(Pr,C_6): a yellow oil, yield 56 mg (65%). Anal. Calcd for $C_{24}H_{38}N_4O_2 \cdot 0.5CH_3OH$: C, 68.33; H, 9.36; N, 13.01. Found: C, 67.94; H, 9.14; N, 13.18.

(n) 1,10-Dioxo-2,9,15,23-tetraaza-12,15,23,26-tetrahydro[10.6]metacyclophane, cBisNAH(C_6,C_6): a yellow solid, yield 74 mg (86%). Anal. Calcd for $C_{24}H_{36}N_4O_2 \cdot 2CH_3OH$: C, 65.52; H, 9.30; N, 11.75. Found: C, 65.67; H, 9.22; N, 12.08.

(o) 1-Propyl-3-(N-propylcarbamoyl)-1,4-dihydropyridine, (N-Pr)PNAH: a yellow oil, yield 69 mg (80%). Anal. Calcd for $C_{12}H_{20}N_2O \cdot 0.33CH_3OH$: C, 67.65; H, 9.82; N, 12.79. Found: C, 67.29; H, 9.34; N, 12.95.

(p) 1-Benzyl-3-[N-(β-(3-indolyl)ethyl)carbamoyl]-1,4-dihydropyridine, (N-Et-I)BNAH: a yellow oil, yield 46 mg (51%); M_r 357.45, M^+ *m/e* 357.[43]

Reduction of Hexachloroacetone. A solution of BisNAH(C_6,Bzl) (10 mg, 2.0×10^{-5} mol) and hexachloroacetone (30 μL, 2.0×10^{-4} mol) in dichloromethane (500 μL) was allowed to stand for ca. 10 h at room temperature in a sealed tube. Then, the reaction mixture was shaken upon addition of aqueous hydrochloric acid (1 M, 200 μL). Gas chromatographic analysis of the organic layer confirmed the quantitative formation of 1,1,1,3,3,3-hexachloro-2-propanol, on the basis of the amount of BisNAH(C_6,Bzl) used, for six different runs. The reaction of BisNAH(C_6,Bzl) (28 mg, 5.4×10^{-5} mol) and the ketone (50 μL, 3.3×10^{-4} mol) was carried out in dichloromethane (1 mL) for 2.5 h in a similar manner. At the end of the reaction, deuterium oxide (300 μL) containing sodium 4,4-dimethyl-4-silapentane-5-sulfonate (DSS, 3 mg) and potassium chloride (9 mg, 1.2×10^{-4} mol) was added to the reaction

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mixture. The NMR spectrum for the aqueous layer showed signals exclusively attributable to BisNA$^+$(C_6,Bzl), the yield being quantitative as confirmed by HPLC analysis.

The reaction behavior was monitored by ^{1}H NMR spectroscopy. Into a solution of BisNAH(C_6,Bzl) (25 mg, 5.0×10^{-5} mol) in deuteriochloroform (200 μL), containing 1% acetonitrile as an internal reference in an NMR tube, was added an equimolar amount of hexachloroacetone (7 μL, 5.0×10^{-5} mol), i.e., the ketone in 0.5 equiv to the dihydronicotinamide unit. After the reaction mixture was allowed to stand at room temperature for 2 h, ^{1}H NMR signals for BisNAH(C_6,Bzl) disappeared completely on one hand and a proton signal attributable to the 2-proton of the alcohol product (4.81 ppm downfield from Me_4Si) was observed on the other. The signal intensity indicated quantitative formation of the alcohol. The reaction of (*N*-Et)BNAH (44 mg, 1.8×10^{-4} mol) with the ketone (13.5 μL, 9.0×10^{-5} mol) was carried out in a similar manner in deuteriochloroform (250 μL), containing 1% acetonitrile, at room temperature. The resulting NMR spectrum indicated that the alcohol product was formed quantitatively, and a half of the initial amount of (*N*-Et)BNAH was consumed.

Kinetic Measurements. Each run was initiated by injecting hexachloroacetone (4.5 μL, 3.0×10^{-5} mol) into a solution (3 mL) of an appropriate 1,4-dihydronicotinamide, which was preequilibrated at 25.0 ± 0.1 °C in a thermostated 1-cm quartz cell set in the spectrophotometer. The initial concentrations of dihydronicotinamides were maintained constant at 1.0×10^{-4} M for monodihydronicotinamides and at 5.0×10^{-5} M for bis(dihydronicotinamide)s, so that the total concentrations in terms of the dihydronicotinamide unit were adjusted at 1.0×10^{-4} M. Progress of the reaction was monitored spectrophotometrically by measuring the absorbance decay at 350 nm, which is referred to consumption of the dihydronicotinamide moiety. Control experiments indicated that no reaction took place in the absence of the ketone. Hexachloroacetone did not undergo any spontaneous decomposition in the solvents employed here, as confirmed by electronic spectroscopy. For kinetic runs under anaerobic conditions, all the solutions placed in a specially designed cell were purged with argon just before injection of the ketone.

Registry No. **1**, 10400-19-8; **2a**, 39642-79-0; **2b**, 73041-73-3; **2c**, 77091-29-3; **2d**, 77091-31-7; **3**, 4314-66-3; **4**, 51055-31-3; BisNA$^+$(C_4,Bzl), 82352-73-6; BisNA$^+$(C_6,Bzl), 81408-01-7; BisNA$^+$(C_8,Bzl), 82352-74-7; BisNA$^+$(C_{10},Bzl), 82352-75-8; BisNA$^+$(Et,*p*-xyl), 82352-76-9; BisNA$^+$(Et,*m*-xyl), 82352-77-0; BisNA$^+$(Et,*o*-xyl), 82352-78-1; cBisNA$^+$(C_4,*p*-xyl), 82352-79-2; cBisNA$^+$(C_6,*p*-xyl), 82352-80-5; cBisNA$^+$(C_6,*p*-xyl), 82352-81-6; BisNA$^+$(C_6,Pr), 82352-82-7; BisNA$^+$(Pr,C_6), 82352-83-8; cBisNA$^+$(C_6,C_6), 82352-84-9; (*N*-Et)BNA$^+$, 81388-57-0; (*N*-Pr)PNA$^+$, 82352-85-0; (*N*-Et-I)BNA$^+$, 82352-86-1; PNAH, 17750-24-2; NAH-C_6-Ad, 27474-83-5; BisNAH(C_4,Bzl), 78857-79-1; BisNAH(C_6,Bzl), 78844-34-5; BisNAH(C_8,Bzl), 78844-35-6; BisNAH(C_{10},Bzl), 78844-36-7; BisNAH(Et,*p*-xyl), 78844-37-8; BisNAH(Et,*m*-xyl), 82352-87-2; BisNAH(Et,*o*-xyl), 82352-88-3; cBisNAH(C_4,*p*-xyl), 82352-89-4; cBisNAH(C_6,*p*-xyl), 78857-80-4; cBisNAH(C_4,*o*-xyl), 82352-90-7; *N*-EtBNAH, 78844-38-9; BisNAH(C_6,Pr), 82352-91-8; BisNAH(Pr,C_6), 82352-92-9; cBis(C_6,C_6), 82352-93-0; (*N*-Et-I)PNAH, 82352-94-1; (*N*-Et-I)BNAH, 82352-95-2; α,ω-diaminobutane, 110-60-1; α,ω-diaminohexane, 124-09-4; α,ω-diaminooctane, 373-44-4; α,ω-diaminodecane, 646-25-3; benzyl chloride, 100-44-7; *p*-xylylene dichloride, 623-25-6; *o*-xylylene dibromide, 91-13-4; *n*-propyl iodide, 107-08-4; 1,6-diiodohexane, 629-09-4; hexachloroacetone, 116-16-5.

Carrier-Mediated Transport of Amino Acid and Simple Organic Anions by Lipophilic Metal Complexes

Kazuhiro Maruyama,*† Hiroshi Tsukube,*‡ and Takeo Araki§

Contribution from the Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan, the Department of Chemistry, College of Liberal Arts and Science, Okayama University, Okayama 700, Japan, and the Department of Chemistry, Faculty of Science, Shimane University, Matsue 690, Japan. *Received March 30, 1981*

Abstract: A variety of lipophilic metal complexes were examined as a new type of anion-transport carrier in a methylene chloride liquid membrane system. Some copper complex carriers, composed of neutral ligands, could effectively mediate active and passive transport of simple organic anions and amino acid derivatives. Their transport properties were largely different from those of previously reported organic anion carriers and were essentially dependent on the combined characteristics of ligand molecule, coordinated metal ion, antiport anion, and others. Liquid–liquid extraction experiments of each elementary process clearly demonstrated that the overall transport rate was mostly determined by that of the substrate-releasing process from the membrane. Active transport of biologically important amino acid derivatives was successfully achieved by this type of carrier, providing a new chemical analogue to some biological transport systems.

Membrane transport is a fundamental and essential process in many biological systems, and its model systems have actively been studied. Of particular, many kinds of synthetic carriers such as crown ethers[1] and cryptands[2] have been utilized as potential carriers for transporting alkali metal and organic ammonium cations and permitted the successful resolution of some racemates into the optically active forms.[3] In marked contrast, little attention has been directed toward transport of anionic species such as amino acids (carboxylate, phenolate, and thiolate anions) and ATP (phosphate anion), which are important from the biochemical and medical points of view. Hence, development of a new type of carrier capable of transporting these organic anions is required not only to simulate many biological systems but also to create a new methodology in separation science.

Recently some host molecules have been prepared,[4] but we know of only a few successful examples of carrier-mediated transport of organic anions.[5] Lehn et al. and Tabushi et al. have presented

† Kyoto University.
‡ Okayama University.
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