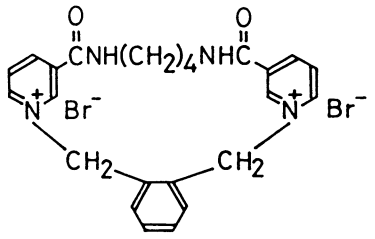
CHEMISTRY LETTERS, pp. 1565-1568, 1983.

MULTICENTER ORGANIC REDOX SYSTEM. NOVEL REDUCTION OF BISNICOTINAMIDES AS ENHANCED BY INTRAMOLECULAR FACE-TO-FACE GEOMETRY

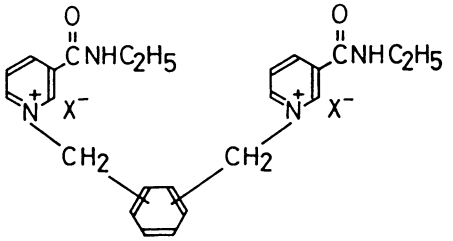
Yukito MURAKAMI,* Jun-ichi KIKUCHI, and Koji NISHIDA
Department of Organic Synthesis, Faculty of Engineering, Kyushu University,
Hakozaki, Higashi-ku, Fukuoka 812

The cyclic "face-to-face" bisnicotinamide, cBisNA$^+$(C_4,o-Xyl), and its noncyclic counterpart, BisNA$^+$(Et,o-Xyl), were readily reduced with the hydroxide ion to afford intramolecular 6,6'-coupling products. The effect of rigid intramolecular geometry on the reactivity was discussed in reference to the similar geometrical effect given by bisdihydronicotinamides on the reduction of a carbonyl substrate.

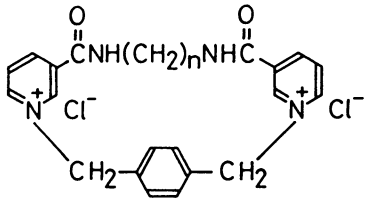
In connection with the biological redox systems, much attention has been focused on the development of catalysts which promote multi-electron transfer reactions. Some metal complexes having two redox sites intramolecularly, such as binuclear cryptates[1] and face-to-face metalloporphyrin dimers,[2] have been noted as such catalysts. However, organic systems involving multiple redox sites have little been investigated up to the present time. We have shown previously that the intramolecular electronic interaction between two dihydronicotinamides gives out large kinetic effects in the reduction of hexachloroacetone.[3] Thus, it became important to clarify the redox behavior of bisnicotinamides from the viewpoint of oxidation efficiency. In the present work, the intramolecular



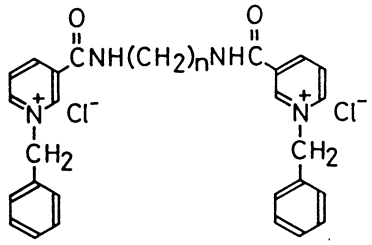
cBisNA$^+$(C_4,o-Xyl)



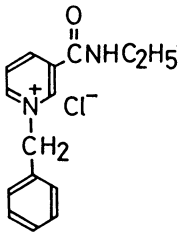
BisNA$^+$(Et,x-Xyl)
x = p (X=Cl); x = m,o (X=Br)



cBisNA$^+$(C_n,p-Xyl)
n = 4,6



BisNA$^+$(C_n,Bzl)
n = 4,6



(N-Et)BNA$^+$

face-to-face geometry as regards the arrangement of nicotinamide moieties was found to enhance the reduction of bisnicotinamides.

In aqueous alkaline media (pH 12) at room temperature, the face-to-face bisnicotinamide, cBisNA$^+$-(C_4,o-Xyl),[3b] was instantaneously reduced with the hydroxide ion to afford the intramolecular 6,6'-coupling product (D in Scheme 1).[4] The product was identified on the following ground. (i) The reaction was found to take place exclusively on the pyridinium rings as confirmed by IR.[5] (ii) UV absorption maxima at 350 (ε 4400) and 258 nm (ε 19000) in water indicate that the 1,6-dihydropyridine moieties are formed through 6,6'-coupling reaction.[6] (iii) The UV absorption spectrum is comparable to that of the intramolecular 6,6'-adduct of 1,1'-ethylenebis(3-carbamoylpyridinium bromide) as produced by electrochemical means; λ_{max} (0.1 mol dm^{-3} phosphate buffer, pH 7.2) 350 (ε 5900) and 275 nm (ε 17000).[7] In addition, the present product showed a new band at around 300 nm along with disappearance of the band at 350 nm in acidic media. This spectral change is presumably attributed to the addition of water to the 4-5 double bond as confirmed for the reference 6,6'-adduct.[7] (iv) ^{1}H-NMR data are consistent with the structure represented by D (Scheme 1):[8,9] in DMSO-d_6 with TMS as an internal reference; δ 7.35 (4H, m, phenyl H's), 6.12 (2H, d, pyridine 4-H), 5.20 (2H, s, pyridine 2-H), 5.12 (2H, q, pyridine 5-H), 4.12 (4H, s, NCH_2), 3.3-3.0 (6H, m, $CONHCH_2$ and pyridine 6-H), and 1.40 (4H, m, other methylene H's). (v) The 6,6'-dimer derived from 1-benzyl-3-carbamoylpyridinium chloride have been found to reduce some electron-deficient substrates such as 2,6-dichloroindophenol[6] and chloranil.[9] The present product showed a similar reduction capability. (vi) Hydrogen peroxide was detected in the reaction mixture by iodometric analysis (some 2% yield on the basis of an amount of cBisNA$^+$(C_4,o-Xyl)).[10]

Apparent first-order rate constants for the 6,6'-coupling reaction were determined by measuring the absorbance change at 350 nm (Table 1). It has been reported that the pyridinium ring of electron-deficient nature readily undergoes addition reaction with various nucleophiles and the hydroxide ion is taken into the pyridinium species to yield the corresponding pseudo-base.[11] The face-to-face bisnicotinamide, cBisNA$^+$(C_4,o-Xyl), yielded exclusively the 6,6'-coupling product even in the presence of cyanide or n-butylamine, while other bisnicotinamides such as cBisNA$^+$(C_4,p-Xyl), BisNA$^+$-(Et,p-Xyl), and BisNA$^+$(C_6,Bzl) underwent addition reaction with these nucleophiles under the same conditions. The formation of pseudo-bases was hardly detected in the reaction of the mono- and bis-

Table 1. Pseudo-first-order rate constants of the intramolecular 6,6'-coupling reaction at pH 11.5 and reduction potentials for nicotinamides at 25.0 °C

Nicotinamide	$k^{a)}$/min^{-1}	$E_p^{b)}$/V vs. SCE
cBisNA$^+$(C_4,o-Xyl)	2.90 (0.11)[c)]	-0.90
BisNA$^+$(Et,o-Xyl)	0.50	-0.95
BisNA$^+$(Et,m-Xyl)	____[d)]	-1.10
(N-Et)BNA$^+$	____[d)]	-1.13

a) Concentration of a nicotinamide (NA$^+$) unit: 4.0 x 10^{-5} mol dm^{-3}. b) Peak potential of the first reduction wave as measured by cyclic voltammetry with a glassy carbon electrode in 0.2 mol dm^{-3} aqueous phosphate buffer: pH 7.0; ionic strength, 0.5 with potassium chloride; concentration of NA$^+$ unit, 1.0 x 10^{-3} mol dm^{-3}; scan rate, 10 mV s^{-1}. c) Potassium chloride (2.0 mol dm^{-3}) added. d) No reaction.

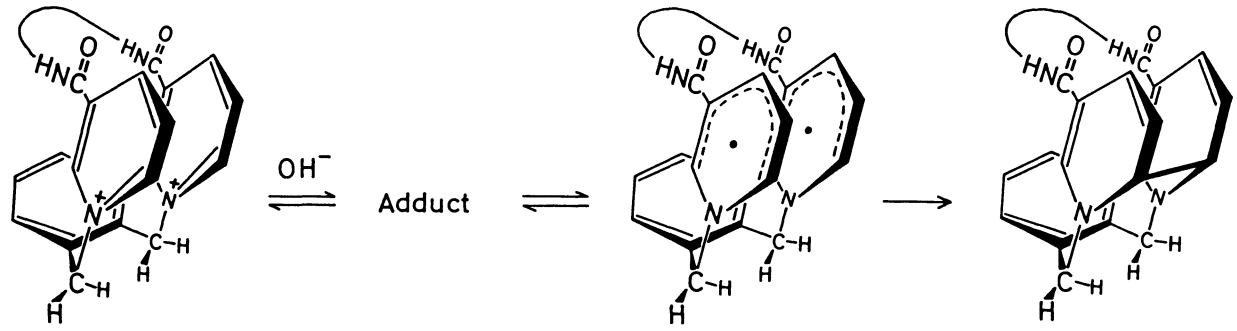
nicotinamides of the present study with the hydroxide ion at pH 12. However, the pseudo-base formation must primarily be determining the overall reaction rate in the light of an experimental evidence that the rate of 6,6'-coupling reaction with cBisNA$^+$(C_4,o-Xyl) was much reduced in the presence of a large amount of potassium chloride (2.0 mol dm^{-3}) as shown in Table 1.

It needs to be pointed out that the reactivity for the novel 6,6'-coupling reaction is rigorously dependent on the molecular geometry of bisnicotinamides. Although both cBisNA$^+$(C_4,o-Xyl) and BisNA$^+$(Et,o-Xyl)[3b] underwent the 6,6'-coupling reaction in a similar manner as judged from their spectral changes, other nicotinamide derivatives[3b] such as cBisNA$^+$(C_n,p-Xyl) (n = 4, 6), BisNA$^+$-(Et,x-Xyl) (x = m, p), and BisNA$^+$(C_n,Bzl) (n = 4, 6) and a mononicotinamide, (N-Et)BNA$^+$,[3b] did not show any reaction to occur under the same conditions. As regards these inert nicotinamide derivatives, the two nicotinamide moieties obviously cannot take tight intramolecular face-to-face geometry. The reduced form of BisNA$^+$(C_n,Bzl), BisNAH(C_n,Bzl), was claimed to place its nicotinamide groups in face-to-face conformation if n = 4 or 6 during the reaction with hexachloroacetone in dichloromethane on the basis of kinetic study and examination of its CPK molecular model.[3b] However, BisNA$^+$(C_n,Bzl) presumably does not take face-to-face conformation of the nicotinamide moieties due to effective solvation of them in aqueous media. The nicotinamide groups of cBisNA$^+$(C_4,o-Xyl) may assume face-to-face conformation much tighter than those of its noncyclic counterpart, so that any water molecules cannot be inserted between these groups of the former. Since the reactivity of cBisNA$^+$(C_4,o-Xyl) is 5.8 times as large as that of the noncyclic counterpart (Table 1), the extent of face-to-face arrangement of the two nicotinamide moieties is clearly reflected on the reactivity.

The reactivity of nicotinamide derivatives in the 6,6'-coupling reaction is reasonably correlated with the electrochemical reduction potential for them. Table 1 summarizes peak potentials of some nicotinamides for the first reduction wave, which corresponds to one-electron reduction of a nicotinamide ring to give the corresponding radical species.[12] cBisNA$^+$(C_4,o-Xyl) is apparently the most effective oxidizing agent. The peak potential is also subjected to change by the relative geometry of nicotinamide moieties.

The reaction mechanism for 6,6'-coupling is proposed here on the basis of the above results as shown in Scheme 1: initial formation of the pseudo-base of a nicotinamide (A) formed with the hydroxide ion is followed by its conversion into the biradical (R) and the 6,6'-coupling reaction which is subjected to the solvent cage effect to afford the product (D). Since the overall reaction was not affected by the atmospheric conditions, aerobic or anaerobic, the odd electrons in R must be effectively delocalized throughout the molecule. In the light of the reaction mechanism given here, the reac-

Scheme 1.



cBisNA$^+$(C_4,o-Xyl) A R D

tion is definitely favored by the face-to-face arrangement of the two nicotinamide rings, which may give out the following effects: (i) the formation of the pseudo-base is enhanced through the intramolecular electronic interaction between the rings, even though the life time of A would be very short; (ii) effective delocalization of odd electrons is attained throughout the whole molecule (R); and (iii) the intramolecular coupling reaction is enhanced in a solvent cage. In the light of the present results, it is reasonable to suggest that the oxidation reactions of substrates with NAD^+ models proceed through multi-step mechanisms.[13]

References

1) J.-M. Lehn, S. H. Pine, E. Watanabe, and A. K. Willard, J. Am. Chem. Soc., 99, 6766 (1977); A. H. Alberts, R. Annunziata, and J.-M. Lehn, ibid., 99, 8502 (1977).
2) N. E. Kagan, D. Mauzerall, and R. B. Merrifield, J. Am. Chem. Soc., 99, 5484 (1977); J. P. Collman, P. Denisevich, Y. Konai, M. Marrocco, C. Koval, and F. C. Anson, ibid., 102, 6027 (1980); M. H. Hatada, A. Tulinsky, and C. K. Chang, ibid., 102, 7115 (1980).
3) a) Y. Murakami, Y. Aoyama, and J. Kikuchi, J. Chem. Soc., Chem. Commun., 1981, 444; b) Y. Murakami, Y. Aoyama, J. Kikuchi, and K. Nishida, J. Am. Chem. Soc., 104, 5189 (1982).
4) Yellow precipitates were produced in the aqueous solution (11 ml) of $cBisNA^+(C_4,o\text{-Xyl})$ (20 mg) at pH 12.1; yield 10 mg.
5) IR (KBr): 3310 and 3240 (NH), 3040 (benzene ring), 2900 and 2840 (CH), and 1655 cm^{-1} (C=O); bands due to the vibrational modes of pyridinium ring observed for $cBisNA^+(C_4,o\text{-Xyl})$ at 3060, 745, 690, and 665 cm^{-1} disappeared.
6) Among the three isomeric dihydropyridines formed from nicotinamides, the 1,6-dihydro species is characterized by two UV bands in the ranges of 270 and 360 nm; K. Wallenfels and M. Gellrich, Chem. Ber., 92, 1406 (1959).
7) D. J. McClemens, A. K. Garrison, and A. L. Underwood, J. Org. Chem., 34, 1867 (1969).
8) K. Kano and T. Matsuo, Bull. Chem. Soc. Jpn., 49, 3269 (1976).
9) S. Kato, J. Nakaya, and E. Imoto, Rev. Polarography, 18, 29 (1972).
10) Further attack of the hydroxyl radical generated along with the formation of R on the product (D) seems to be responsible for the low yield of H_2O_2. In fact, the product consisted of two components as detected by TLC. In any case, however, the product is definitely the 6,6'-coupled one as confirmed by the spectroscopic means.
11) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York (1966), Vol. 2, p. 181.
12) K. S. V. Santhanam and P. J. Elving, J. Am. Chem. Soc., 95, 5482 (1973).
13) D. M. Stout and A. I. Meyers, Chem. Rev., 82, 223 (1982).

(Received June 30, 1983)