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Bis-1,4-dihydronicotinamides. Intramolecular Electronic Interaction and Its Consequence in the Reduction of a Carbonyl Substrate in Aprotic Solvents

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Summary The reduction of hexachloroacetone in CH_2Cl_2 or $CHCl_3$ was much enhanced in the presence of 1,6-bis(1-benzyl-1,4-dihydronicotinamido)hexane owing to an intra-

molecular electronic interaction of charge transfer character.

THE use of 1-alkyl-1,4-dihydronicotinamides as co-enzyme NAD(P)H models is a subject of considerable interest. Although much attention has been paid to the activation of substrates,¹ the activation of the dihydronicotinamide species *via* electronic perturbation has been little studied.² We have investigated the reactivities of several bis-1,4-dihydronicotinamides (HNA-HNA) in the reduction of a carbonyl substrate in order to evaluate the kinetic consequences of the intramolecular nicotinamide-nicotinamide interaction.



The reduction of hexachloroacetone with HNA-HNA (1b) took place readily in CH_2Cl_2 or $CDCl_3$ and gave the oxidized bisnicotinamide salt (NA⁺-NA⁺) (as identified by ¹H n.m.r. and h.p.l.c.) and 1,1,1,3,3,3-hexachloropropan-2-ol in 100% yield based on the amount of (1b), confirmed by g.l.c. (for CH_2Cl_2 solution) and ¹H n.m.r. analysis (for $CDCl_3$ solution).³ When a large excess of the substrate in CH_2Cl_2 was used, the rate of disappearance of the characteristic absorption band of (1b) at 350 nm was much greater than those of its mononicotinamide counterparts (4a) and (4b) (Table).

 TABLE.
 Reactivities^a of 1,4-dihydronicotinamides in the reduction of hexachloroacetone.^b

Nicotinamide	In CH ₂ Cl ₂	In CH ₃ CN
(1a)	55	120
(1b)	40	110
(1 c)	150	110
(1d)	255	
(2)	160	155
(3)	1100	120
(4 a)	4000	260
(4b)	1200	120

^a Given in half-life ($t_{\frac{1}{2}}$ /s) as measured by the disappearance of the 350 nm absorbance of 1,4-dihydronicotinamides under aerobic conditions. ^b [HNA unit], 1.0×10^{-4} mol dm⁻³; [(Cl₃C)₂CO], 1.0×10^{-2} mol dm⁻³; at 25.0 \pm 0.1 °C.

When the reaction medium was deoxygenated prior to the initiation of reaction, the initial rapid loss of absorbance intensity at 350 nm up to about 50% [owing to reaction of (1b) with the added substrate] was followed by much slower rate of absorbance decay. On the other hand, the reaction of (4b) showed practically no difference under aerobic and anaerobic conditions.

The solvent effect on the reactivity of (1b) is noteworthy (Table); a change of solvent from CH_2Cl_2 to more polar CH_3CN resulted in a 3-fold decrease in reactivity. This is in marked contrast with the solvent effect on the reactivity of (4b); 10-times more reactive in CH_3CN than in CH_2Cl_2 . Thus, the acceleration factor of (1b) over (4b) is 1:1 in CH_3CN , 30:1 in CH_2Cl_2 , and even greater in the less polar $CHCl_3$ (50:1).

Reaction of a non-degassed, equimolar mixture of (1b) and hexachloroacetone in CDCl_3 (*i.e.* ketone: HNA unit = 0.5: 1) yielded NA⁺-NA⁺ (by ¹H n.m.r. spectroscopy), *i.e.* one HNA unit in (1b) undergoes oxidation without participation of the ketone. In contrast, (4b) reacts on a 1:1 basis with the ketone. In each case formation of the alcohol product is nearly quantitative.

These results, taken together with the difference in reaction rates of (1b) in CH_2Cl_2 under aerobic and anaerobic conditions, allow predictions to be made about the mechanism in such solvents under aerobic conditions (Scheme).



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The initial reaction (rate constant k_1) is associated with the reduction of the substrate without participation of dioxygen and the resulting intermediate (HNA-NA+) undergoes a facile oxidation with dioxygen (rate constant k_2). [In the absence of the ketone, (1b) in CH_2Cl_2 was stable even under an aerobic atmosphere.] The significant increase in k_1 , the facile oxidation of HNA-NA+, and the specific solvent effect thereupon may be interpreted in a unified manner by postulating an electronic interaction of charge transfer character in HNA-NA+ and also in the transition state of its formation (Scheme). The intermolecular charge transfer interaction between reduced (HNA) and oxidized (NA+) nicotinamide⁴ and an electron transfer between them giving rise to a radical pair⁵ have been demonstrated. Relatively higher concentrations of HNA and NA⁺ are apparently required for these intermolecular processes.

The relative reactivity of HNA-HNA is quite sensitive to the intramolecular geometrical arrangement of the two nicotinamide units. A non-cyclic HNA-HNA (3), having a rigid p-xylylene bridge, is a simple, functionally identical analogue of (4b) (Table). Its cyclic counterpart (2) shows only a moderate catalytic reactivity, despite the fact that two nicotinamide units are intramolecularly fixed so as to minimize conformational allowance. The variation of polymethylene chain length in (1; n = 4, 6, 8, and 10) is sensitively reflected in the reactivity, the maximal reactivity being observed for n = 6. In conclusion, a close face-toface conformation for the two nicotinamide units seems to be the primary requirement for an electronic interaction of kinetic significance.

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¹ E.g. D. J. Creighton, J. Hajdu, and D. S. Sigman, J. Am. Chem. Soc., 1976, 98, 4619; U. K. Pandit and J. R. Mas Cabre, Chem. Commun., 1971, 552; S. Shinkai and T. C. Bruice, J. Am. Chem. Soc., 1972, 94, 8258; P. van Eikeren and D. L. Grier, *ibid.*, 1976, 98, 4655; S. Shinkai, H. Hamada, Y. Kusano, and O. Manabe, J. Chem. Soc., Perkin Trans. 2, 1979, 699. ² J. Hajdu and D. S. Sigman, J. Am. Chem. Soc., 1975, 97, 3524. ³ For the reduction of hexachloroacetone with (4a) and its derivatives in CH₃CN, see: D. C. Dittmer, A. Lombardo, F. Batzold, and

^c Por the reduction of nexatino oracetonic with (4a) and its derivatives in Origon, sec. D. S. Eneme, 12 Description, 12 Descriptio