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

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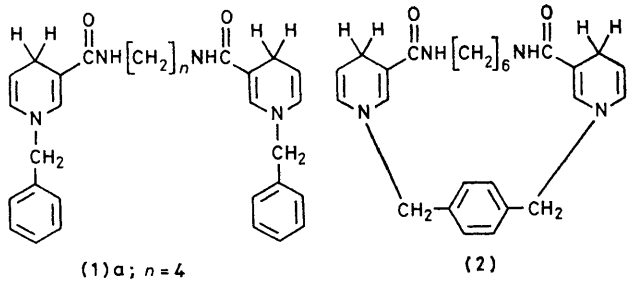
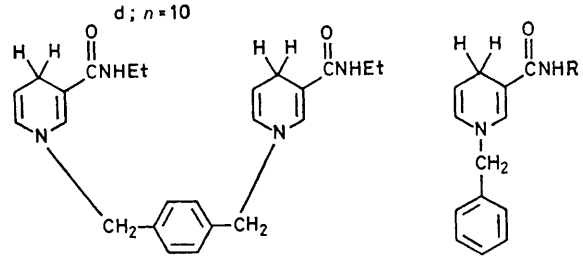
Summary The reduction of hexachloroacetone in CH_2Cl_2 or $CHCl_3$ was much enhanced in the presence of 1,6-bis(1-benzyl-1,4-dihydronicotinamido)hexane owing to an intramolecular electronic interaction of charge transfer character.

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.



(1) a; $n = 4$
b; $n = 6$
c; $n = 8$
d; $n = 10$

(2)



(3)

(4) a; R = H
b; R = Et

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_2Cl_2	In CH_3CN
(**1a**)	55	120
(**1b**)	40	110
(**1c**)	150	110
(**1d**)	255	
(**2**)	160	155
(**3**)	1100	120
(**4a**)	4000	260
(**4b**)	1200	120

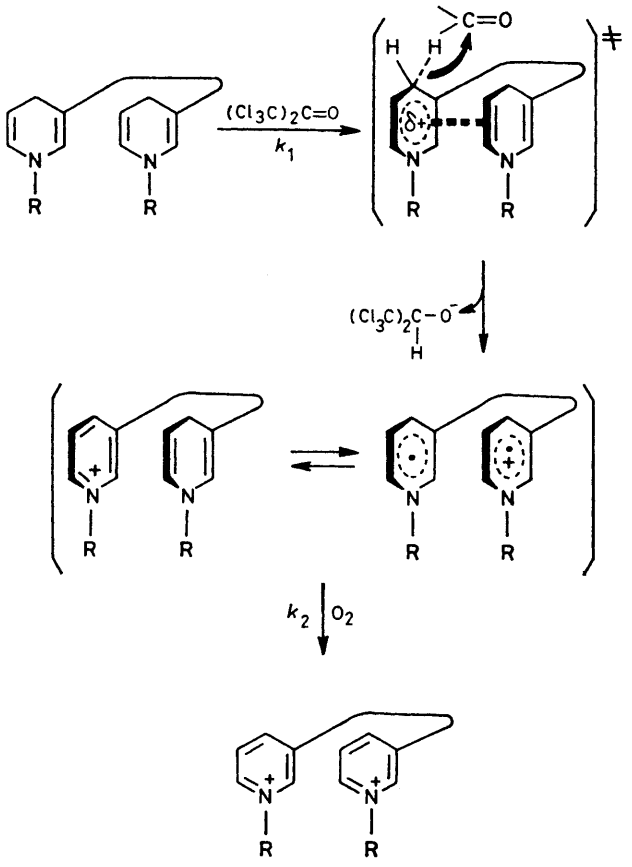
[a] Given in half-life ($t_{\frac{1}{2}}$/s) as measured by the disappearance of the 350 nm absorbance of 1,4-dihydronicotinamides under aerobic conditions. [b] [HNA unit], $1{\cdot}0 \times 10^{-4}$ mol dm^{-3}; $[(Cl_3C)_2CO]$, $1{\cdot}0 \times 10^{-2}$ mol dm^{-3}; at 25·0 ± 0·1 °C.

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).



(R = CH_2Ph)

SCHEME

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^+) nicotinamide[4] and an electron transfer between them giving rise to a radical pair[5] 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-to-face conformation for the two nicotinamide units seems to be the primary requirement for an electronic interaction of kinetic significance.

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[3] For the reduction of hexachloroacetone with (**4a**) and its derivatives in CH_3CN, see: D. C. Dittmer, A. Lombardo, F. Batzold, and C. S. Greene, *J. Org. Chem.*, 1976, **41**, 2976.

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