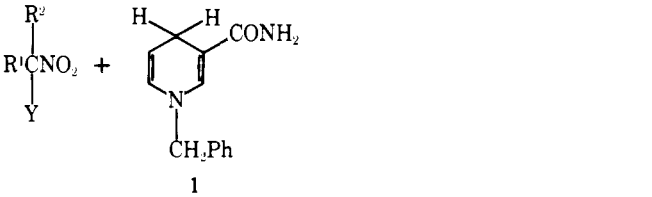
1-Benzyl-1,4-dihydronicotinamide as a Reagent for Replacing Aliphatic Nitro Groups by Hydrogen: An Electron-Transfer Chain Reaction

Sir:

1-Benzyl-1,4-dihydronicotinamide (BNAH) is of interest as a model of the biochemically important reduced nicotinamide-adenine dinucleotide phosphate [NAD(P)H] and, also, because it has been shown to reduce a very wide variety of organic compounds.[1] Most of these reductions are believed to proceed by a hydride-transfer mechanism.[2]

We now describe a new reaction of BNAH (**1**)—the replacement of an aliphatic nitro group by hydrogen (eq 1).[3]



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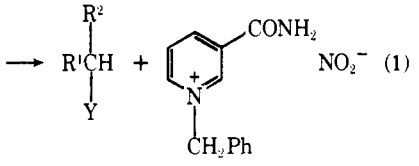
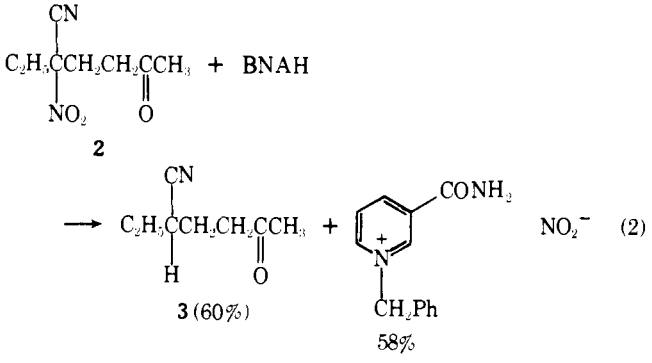


(1)

Y = CN, COOR; R¹ = Me or Et;
R² = CH_2CH_2[C(O)CH_3, CN, $COOCH_3$]
Y = C(O)Ar; R¹ = Me; R² = Me or H

Although the reaction of eq 1 requires the presence of a cyano, carboalkoxy, or keto group on the carbon undergoing substitution, it appears that in some cases it may prove to be of special value, e.g., the reaction of eq 2.[4] The utility of this



2

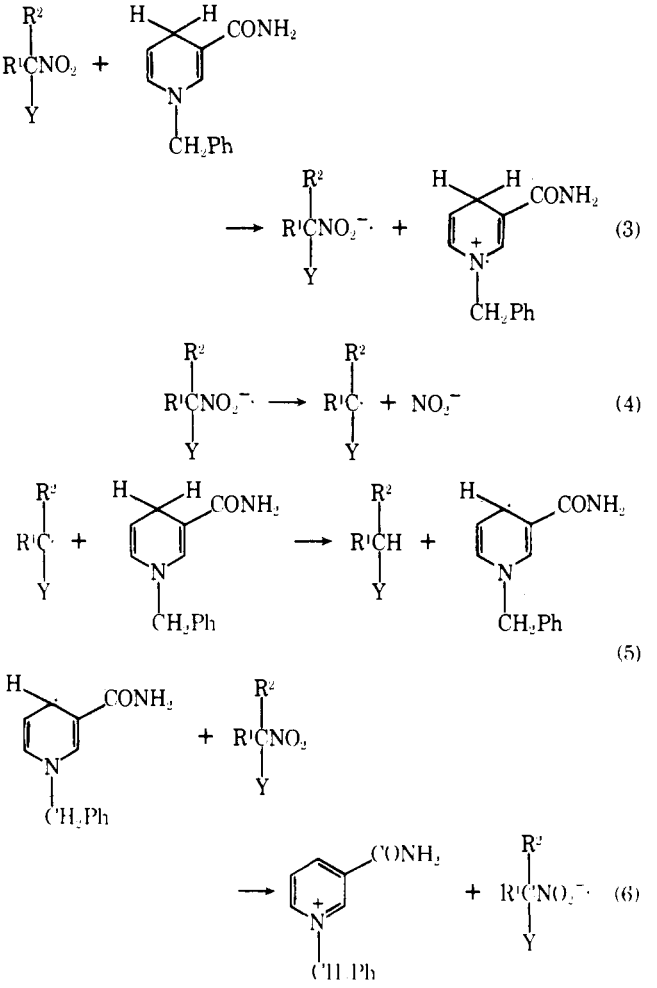
3 (60%)

58%

(2)

method of replacing nitro by hydrogen is indicated by the results summarized in Table I.

The matter of mechanism is of special interest. Previous discussions of reductions by BNAH have focussed on the ability of BNAH to act as a hydride-transfer agent. We propose that here BNAH replaces the nitro group by hydrogen via an electron-transfer chain mechanism (eq 3-6) and present



(3)

(4)

(5)

(6)

evidence in support of this novel mechanistic assignment.

To begin with, these reactions exhibit a strong light effect. They do not occur in the dark, but on exposure to a 150-W tungsten lamp they proceed readily at room temperature. Furthermore, these reactions are inhibited by di-*tert*-butyl nitroxide and *m*-dinitrobenzene. Thus, the reaction of eq 2 is completely inhibited for 6 h by the presence of 20 mol % of di-*tert*-butyl nitroxide; at the end of this time the reaction proceeds at the usual rate. In the absence of the nitroxide the reaction is 85% completed in 6 h. In the same way, the presence of 10 mol % of *m*-dinitrobenzene completely stops the reaction for 6 h, after which time the reaction proceeds, but very slowly.

Table I. Conversion of $O_2NC(Y)(R^1)(R^2)$ into $HC(Y)(R^1)(R^2)$ with BNAH[a]

entry	R^1	R^2	Y	solvent	time, h	isold yield, %[b]
1	C_2H_5	$CH_2CH_2C(=O)CH_3$	CN	benzene	24	60 (97)
2	C_2H_5	$CH_2CH_2COOCH_3$	CN	benzene	24	67 (90)
3	C_2H_5	CH_2CH_2CN	CN	benzene	24	61 (91)
4	CH_3	CH_2CH_2CN	$COOCH_3$	benzene	24	71 (96)
5	CH_3	CH_3	$C_6H_5C=O$	HMPA	24	61 (90)
6	CH_3	CH_3	*p*-$ClC_6H_4C=O$	DMF	24	91
7	CH_3	H	*p*-$ClC_6H_4C=O$	HMPA	48	45 (68)
8	CH_3	H	*p*-$NO_2C_6H_4C=O$	HMPA	48	0[c]
9	CH_3	H	*p*-$CH_3C_6H_4C=O$	HMPA	48	45 (80)

[a] All reactions were carried out at room temperature with exposure to a 150-W tungsten lamp. [b] Spectroscopic and elemental analyses of all products were satisfactory for assigned structures. Yields determined by GLC with internal standard are given in parentheses. [c] Starting material (90%) was recovered.

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Di-*tert*-butyl nitroxide is a free-radical inhibitor[5] and *m*-dinitrobenzene is generally regarded as a scavenger for radical anions.[5] These facts strongly support our contention that the reaction in eq 2 is an electron-transfer chain process.[6,7]

In accord with the proposed mechanism the transformation of eq 2 is induced by electron donors and by free radicals. Thus, although there is no detectable reaction in DMF in the dark at room temperature after 24 h, in the presence of $Na_2S_2O_4$ (3 equiv) none of the nitro compound (**2**) remains after 24 h in the dark at room temperature and a 40% yield of the pure product (**3**) is isolated (65% yield by GLC).[8] Furthermore, in the presence of 8 mol % of di-*tert*-butyl peroxyoxalate[9] the reaction of eq 2 proceeds 61% to completion in the dark in 24 h at room temperature and a 40% yield of pure **3** is isolated. Azobisisobutyronitrile also induces the reaction of eq 2 at 80 °C in the dark; a 50% yield (by GLC) of **3** is obtained after 3 h in the presence of 10 mol % of azobisisobutyronitrile. In the absence of the azo compound a 10% yield of **3** is obtained. This ability of free radicals to induce an electron-transfer chain process is especially noteworthy and should prove of wide applicability.

The experimental procedure for these reduction is illustrated by the reduction of eq 2. A mixture of **2** (1.84 g, 10 mmol) and **1** (6.42 g, 30 mmol) in benzene (150 mL) was stirred for 24 h at room temperature under nitrogen with exposure to a 150-W tungsten lamp. The resulting mixture was washed with 2 N HCl and then with water. The benzene layer was dried over anhydrous magnesium sulfate. Removal of the solvent followed by distillation gave 0.82 g (60% yield) of pure **3**, bp 96 °C (2.8 mmHg).

References and Notes

(1) T. C. Bruice and S. T. Benkovic, "Bioorganic Mechanism", Vol. 2, Benjamin, New York, 1966, and references cited in recent reports. See D. M. Hedstrand, W. M. Kruizinga, and R. M. Kellogg, *Tetrahedron Lett.*, 1255 (1978).

(2) H. Sund in "Biological Oxidation", T. P. Singer, Ed., Wiley-Interscience, Robinson, New York, 1968, pp 621–624. J. J. Steffens and D. M. Chipman, *J. Am. Chem. Soc.*, **93**, 6694 (1971), and references cited therein. Nonchain free-radical mechanisms have been proposed for the reduction of thiobenzophenone by BNAH [A. Ohno and N. Kito, *Chem. Lett.*, 369 (1972)] and for the replacement of the bromine atom of α-bromonitro compounds by BNAH [R. J. Kill and D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 755 (1976)]. However, a recent paper by R. A. Hood, R. H. Prince, and K. A. Rubinson [*ibid.*, 300 (1978)] claims that the detection of free radicals in these reductions by ESR is due to artifacts.

(3) Two other methods for replacing the nitro group by hydrogen have recently been described: the use of the sodium salt of methyl mercaptan at 25 °C [N. Kornblum, S. C. Carlson, and R. G. Smith, *J. Am. Chem. Soc.*, **101**, 647 (1979)] and treatment with KOH in ethylene glycol at 120–140 °C [A. L. Krasuska, H. Piotrowska, and T. Urbanski, *Tetrahedron Lett.*, 1243 (1979)].

(4) Thus, a preliminary attempt to replace the nitro group of compound **2** by hydrogen using $CH_3S^-Na^+$ yielded no product; this may be a consequence of a reverse Michael reaction. Compounds which can be reduced by BNAH are usually more conveniently reduced by other hydride transfer agents such as sodium borohydride, but, with compounds listed in Table I which contain the specified α-nitro group as well as borohydride-reducible groups, BNAH selectively replaces the nitro group by hydrogen without affecting the other functions, while sodium borohydride selectively reduces the borohydride-reducible groups (e.g., keto) without affecting the nitro group. This may be the first case in which BNAH reduces a substrate which is inert to sodium borohydride.

(5) N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **15**, 734 (1975).

(6) Analogous results using 20 mol % of di-*tert*-butyl nitroxide and 10 mol % of *m*-dinitrobenzene have been obtained for the reaction of entry 5 in Table I.

(7) Apropos of the inhibition of *m*-dinitrobenzene, failure of the reaction of entry 8 (Table I) reasonably reflects similar inhibition associated with this substrate's *p*-nitrobenzoyl molety itself.

(8) $Na_2S_2O_4$ is known to be a one-electron-transfer agent; see, for example, P. L. Kolker and W. A. Waters, *J. Chem. Soc.*, 1136 (1964). It is not clear how much of added $Na_2S_2O_4$ is used to induce this reaction, for $Na_2S_2O_4$ is only slightly soluble in DMF. However, **2** is not converted into **3** bn treatment with $Na_2S_2O_4$ in the absence of BNAH.

(9) P. D. Bartlett, E. P. Bezing, and R. E. Pincock, *J. Am. Chem. Soc.*, **82**, 1762 (1960).

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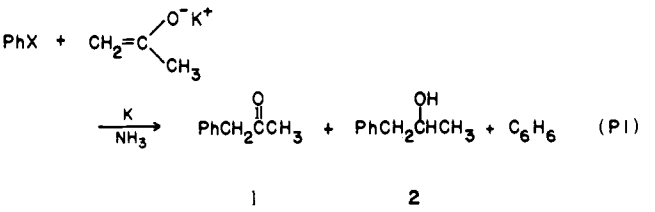
A Major Leaving Group Effect on Chemical Events after the Group Has Left: Reactions of Acetone Enolate Ion with Halobenzenes and Related Substrates Provoked by Solvated Electrons

Sir:

The phenyl halides and like substrates react with potassium acetone enolate and solutions of potassium metal in ammonia to form phenylacetone (**1**), 1-phenyl-2-propanol (**2**), and benzene[1] (eq P1). The proportions depend strongly on the



(P1)

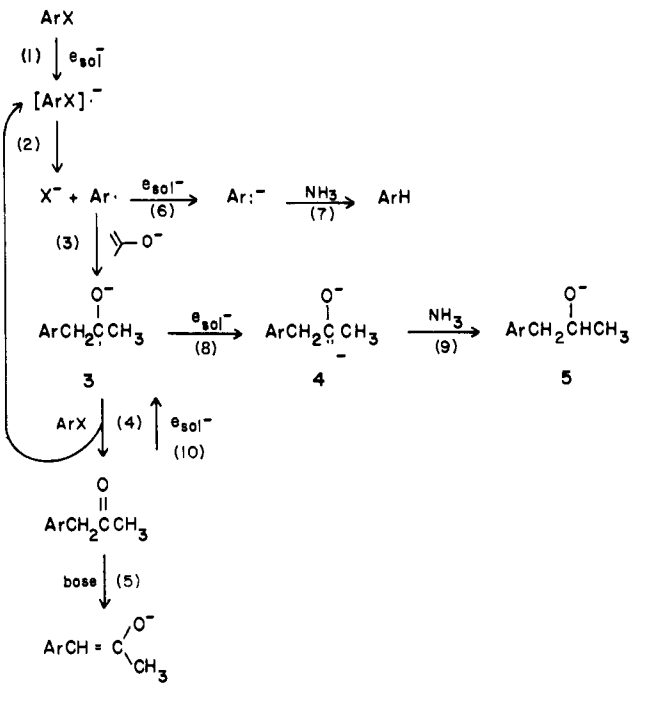
leaving group, as reported in Table I. For example, the ketone/alcohol (**1**/**2**) product ratio is ~7 from PhI but only ~0.6 from PhCl. The proportion of benzene generally is higher when the ketone/alcohol ratio is smaller.

These reactions are believed to occur according to the mechanism sketched in Chart I. This is an elaborated $S_{RN}1$ mechanism;[2] step 1 effects initiation, steps 2, 3, and 4 constitute a propagation cycle, steps 6 and 8 are termination steps, steps 5, 7, and 9 are proton transfers, and step 10 is a familiar type of electron transfer. According to this mechanism, the relative yields of products **1** and **2** are determined primarily by the extents to which steps 4 and 8 are utilized.

It is noteworthy that the leaving group is present in the reactants for steps 4 and 8 only in the electron-accepting ArX for step 4. In an earlier report,[1] it was postulated that the leaving group influences product composition by its effect on the rate of electron transfer from **3** in step 4. We shall present evidence that such is not the case, and therefore that *the leaving group exerts a strong influence on chemical events that occur after its departure from the reacting species.*

The following facts are relevant. (a) Whereas early data[1] afforded a strictly linear plot of log (**1**/**2**) for each halobenzene against the logarithm of the rate constant for its reaction with

Chart I



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