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Abstract

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ORGANIC CATALYSTS. REDUCTION OF FLUORENONE BY 2,6-DIMETHYL-3,5-DICARBOETHOXY-1,4-DIHYDROPYRIDINE

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The possibility of a heterolytic and free-radical mechanism in the reactions of nicotinamide adenine dinucleotide (NAD-H_2) and its models has been discussed repeatedly (^{1,2}). In accordance with the hydride mechanism, activation of the carbonyl group may occur through displacement of the electron density of oxygen toward a metal atom (Zn) (^{3}) or toward an electrophilic group (^{2}) included in the enzyme. For model reactions the hydride mechanism has led to a large number of attempts to reduce carbonyl and olefinic compounds ($^{4-7}$); moreover, enhancement of the electrophilic character of the bonds being reduced was achieved by introducing electron-acceptor substituents. The model reactions carried out thus far for the reduction of carbonyl compounds have not been catalytic.

Until recently, no attempts had been made to use the possibility of free-radical reduction of the carbonyl group. We undertook a search for ways of activating the carbonyl group, based on the ability of dihydropyridine models of NAD-H_2 to react by a free-radical mechanism. In our work (^{8}) on the reduction of some aldehydes and ketones, activation of the carbonyl group was achieved by preliminary preparation of metal ketyls. A mechanism was proposed for the reduction reaction, including one-electron transfer of hydrogen from dihydropyridine to the metal-ketyl molecule.

Table 1

Reduction of fluorenone by means of I in the presence of glucose

No.	Amount of starting substances, mmol: fluorenone	Amount of starting substances, mmol: I	Amount of starting substances, mmol: glucose	Reaction duration, h	Yield of fluorenol, %
1	2	5	–	20	–

No.	Amount of starting substances, mmol: fluorenone	Amount of starting substances, mmol: I	Amount of starting substances, mmol: glucose	Reaction duration, h	Yield of fluorenol, %
2	22	–	22	20	–
3	10	10	20	20	15
4	28	28	28	20	40
5	11	18	11	40	55
6	11	18	3	40	75
7	11	18	0.6	20	35
8	6	12	0.06	40	65
9	4	10	$0.5 \cdot 10^{-3}$	40	70

In the present work we report the reaction, discovered by us, of the catalytic reduction of a carbonyl compound (fluorenone) by the NAD-H_2 model—2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (I). The catalysts of the reaction are certain aldehydes, ketones, and sugars.

Experimental Section

The reduction reaction of fluorenone was carried out at room temperature in an inert atmosphere.

To a 0.5 M solution of sodium ethylate in absolute alcohol were added fluorenone, I, and the catalyst. The mixture was stirred periodically over the course of

tion for 20–40 h, and was then hydrolyzed with water. The following reaction products were isolated: fluorenol with m.p. 151°, lutidinedicarboxylic acid (m.p. 316°; the diethyl ester has m.p. 73°, molecular weight: found 198, calculated 195), and a small amount of saponified dimeric product formed from starting compound I (after recrystallization from isoamyl alcohol it had m.p. 272° with decomposition; molecular weight, determined ebullioscopically, 470; λ_{max} 258 mμ and 350 mμ; elemental analysis: C 55.0%; N 8.0%). Control experiments showed that under the experimental conditions the diethyl ester of lutidinedicarboxylic acid is saponified.

Table 2

Reduction of fluorenone by means of I in the presence of various catalysts

No.	Catalyst: name	Catalyst: amount, mmol	Fluorenone, mmol	I, mmol	Yield of fluorenol, %
1	Formaldehyde	1.5	3	6	70
2	Benzaldehyde	0.1	2	4	60
3	Acetone	0.1	2	4	70
4	Acetophenone	0.1	1	2	47
5	Glyceraldehyde	0.5	4	10	77
6	Ribose	0.6	6	12	48
7	Rhamnose	0.4	4	10	33
8	Glucose	0.06	6	12	65
9	Galactose	0.4	4	10	57
10	Sorbose	0.4	4	10	66
11	Fructose	0.4	4	10	57
12	Lactose	0.3	6	12	83
13	Maltose	0.3	6	12	75
14	Cellobiose	0.2	4	10	73

The experimental data in Tables 1 and 2 show that fluorenone is reduced neither by dihydropyridine in the absence of a catalyst nor by sugars.

Discussion of the results

As can be seen from the data of Tables 1 and 2, formaldehyde, glyceraldehyde, and sugars catalyze the reaction of reduction of fluorenone by dihydropyridine I. In the course of the reaction, more than one mole of dihydropyridine is consumed per mole of reduced fluorenone, apparently as a result of side reactions. We propose the following reaction mechanism (using formaldehyde as an example):

$$\mathbf{1}.\quad \mathrm{HCHO} + \mathrm{C_2H_5O^-} \rightleftharpoons \underset{\mathrm{(II)}}{\mathrm{H{-}C(H)(O^-)(OC_2H_5)}} \xrightleftharpoons{\mathrm{C_2H_5OH}} \mathrm{H{-}C(H)(OH)(OC_2H_5)} + \mathrm{C_2H_5O^-}$$

$$\mathbf{2}.\quad \mathrm{H{-}C(H)(O^-)(OC_2H_5)} + \text{fluorenone} \underset{\mathrm{(III)}}{\longrightarrow} \mathrm{H{-}C(H)(O^\bullet)(OC_2H_5)} + \text{fluorenone}^{\bullet -}$$

$$\mathbf{3}.\quad \text{fluorenone}^{\bullet -} + \mathrm{I} \longrightarrow \text{fluorenolate} + \mathrm{I}^{\bullet +}$$

$$\mathbf{4}.\quad \mathrm{H{-}C(H)(O^\bullet)(OC_2H_5)} + \mathrm{I} \longrightarrow \mathrm{H{-}C(H)(OH)(OC_2H_5)} + \mathrm{I}^{\bullet +}$$

$$\mathbf{5}.\quad \mathrm{I}^{\bullet +} \xrightarrow{\text{dimerization}} \text{dimer}$$

$$\mathrm{I}^{\bullet +} \xrightarrow{(-\mathrm{H}^\bullet)} \text{2,6—dimethyl—3,5—dicarboethoxy—pyridine}$$

Anion II, formed as a result of nucleophilic attack by the alkoxide ion on the carbonyl group of the catalyst, transfers an electron to fluorenone; radical III and the fluorenone ion-radical are thereby formed. The formation of ion-radicals in the reaction of fluorenone with glucose in an alcoholic solution of sodium ethoxide has been shown by the EPR method (9). The fluorenone ion-radical is reduced by dihydropyridine through transfer of a hydrogen atom; fluorenol and the dihydropyridine radical are formed in this process. The latter can dimerize (to a small extent, owing to its low concentration) or be converted into the corresponding pyridine derivative with loss of an H atom. Radical III is reduced by a second molecule of dihydropyridine with formation of a hemiacetal. The anion formed from acetone and acetophenone in the first stage of the reaction has the structure $R—C—CH_2^-$ (10).

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