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Photoinduced reaction of diethyl 2-bromo-1-phenylethylidenemalonate with 1-benzyl-1,4-dihydronicotinamide and the effect of magnesium (II) ion on the reaction

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Abstract

2-Bromo-1-phenylethylidenemalonic ester reacts with 1-benzyl-1,4-dihydronicotinamide (BNAH) in acetonitrile under illumination at $\lambda > 320$ nm to give three debrominated products: an α,β-unsaturated ester, a β,γ-unsaturated ester and a dimer. In the presence of magnesium ion, the β,γ-unsaturated ester is formed exclusively. Using deuterated BNAH-4,4-d_2 as reagent and spin-trapping technique for monitoring reactive intermediate, it has been shown that the reaction proceeds via two different mechanistic pathways: e^- transfer–debromination–H abstraction or dimerization for the formation of the α,β-unsaturated ester and the dimer, and e^- transfer–debromination–e^- transfer–H^+ transfer for the formation of the β,γ-unsaturated ester.

Keywords: Photoinduced reaction; Spin-trapping technique; Magnesium (II) ions

1. Introduction

The mechanism of reduction of various substrates containing the $>\!C{=}O$, $>\!C{=}N{-}$, and $>\!C{=}C\!<$ linkages by reduced coenzyme nicotinamide adenine dinucleotide (NADH) models has been studied by many investigators to mimic the enzymatic processes involving the NADH-dependent enzymes [1–3]. It has been shown that NADH or NADH models can reduce thermally only activated carbonyl compounds, while the excited states of NADH and NADH model compounds can reduce a variety of substrates [4]. There are reports [5] that magnesium and zinc ions catalyze the nonenzymatic reduction of α-keto esters such as that of benzoylformic and pyruvic acid by 1-benzyl-1,4-dihydronicotinamide (BNAH) under very mild conditions, while no reaction occurs in the absence of these metal ions in the dark. Direct transfer of hydrogen is postulated in analogy with the in vivo reduction of carbonyl compounds. Magnesium and zinc ions also catalyze the reduction of (E)-2-, (E)-3-, and (E)-4-cinnamoyl pyridines by BNAH to the corresponding dihydroketones. A mechanism involving a hydride transfer or a sequential transfer of an electron and a hydrogen atom is suggested [6]. Pac and coworkers [7] reported that magnesium ion catalyzes the photosensitized reduction of carbon–carbon double bonds of dimethyl fumarate, derivatives of methyl cinnamate, and some related olefins by BNAH, which proceeds via sequential two electron transfer.

It was reported previously [8] that 2-bromo-1-phenylethylidenemalononitrile was reduced by BNAH in acetonitrile at room temperature in the dark to give 2-phenyl-1,1-cyclopropane dicarbonitrile by a direct hydride transfer mechanism. Kinetic studies [9] on the reduction of 2-bromo-1-(p-X-phenyl)ethylidenemalononitrile (X = H, F, Cl, Br, CN) by BNAH showed that the reaction gave a linear free energy relationship of Hammett equation in consistence with direct hydride transfer mechanism. In order to elucidate the structure and reactivity in the reduction of various substrates by NADH models, we extended the study to the reaction of diethyl 2-bromo-1-phenylethylidenemalonate (**1**) by BNAH (**2**). **1** did not react with BNAH in acetonitrile in the dark, even in the presence of an equivalent amount of magnesium perchlorate at 60°C. Upon irradiation with light of $\lambda > 320$ nm, reaction took place. In this paper, we wish to present the results of this study as well as the effect of added magnesium ion upon the course of reaction.

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2. Experimental details

BNAH was prepared according to the literature [10]. BNAH-4,4-d_2 was prepared according to the method reported in the literature [11], M.W. 216 [mass spectrometry (MS)]; nuclear magnetic resonance (NMR) spectroscopy showed that the hydrogen on C-4 was completely deuterated. 2-Bromo-1-phenylethylidene malonic ester (**1**) was prepared according to the literature [12], M.W. 340 (MS), NMR δ 0.95 (t, 3H, J=7.2 Hz), 1.35(t, 3H, J=7.1 Hz), 4.7(s, 2H), 7.4(s, 5H). Analysis: C, 52.83; H, 5.09. Calcd. for $C_{15}H_{17}O_4Br$: C, 53.94, H, 5.00%. Other reagents were commercial products and were purified by standard procedures where necessary.

Electron spin resonance (ESR) spectra were recorded on a Brucker ER-200 ESR spectrometer. ^{1}HNMR spectra were recorded on a Brucker AM-400 MHz NMR spectrometer.

2.1. Photoinduced experiment

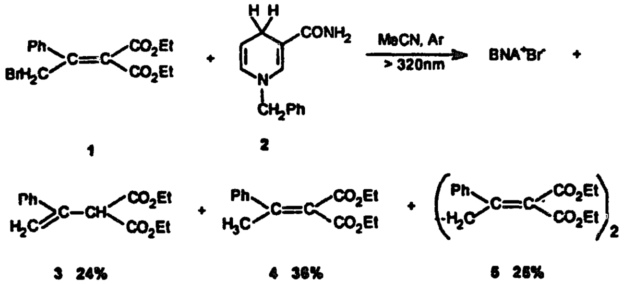
1 (0.035 mmol) and **2** (0.040 mmol) were dissolved in dry acetonitrile (12 ml), which was deaerated by bubbling with argon. The mixture was illuminated with a 500 W high pressure mercury lamp filtered through double layers of glass transmitting light of $\lambda > 320$ nm for 4 h. Over 90% conversion was achieved. The products were isolated by chromatography on a silica column. In the reaction in the presence of magnesium ion, $Mg(ClO_4)_2$ (0.038 mmol) was added to the reaction mixture under otherwise identical condition.

2.2. Spin trapping experiment

BNAH (0.2 mmol) and 2-methyl-2-nitrosopropane (0.1 mmol) were dissolved in 10 ml dry acetonitride and **1** (0.2 mmol) was dissolved in another 10 ml dry acetonitrile. The solutions were bubbled with argon for 5 min and then mixed in equal volume in a tube for irradiation. The mixture was irradiated with a 500 W high pressure mercury lamp for 3 min [1] and then kept in the dark for 1 h. The reaction mixture was measured by ESR spectroscopy.

3. Results and discussion

From the reaction of **1** with **2** under irradiation with light of $\lambda > 320$ nm, four products were obtained as shown in the following scheme:



Product **3**: ^{1}HNMR δ 1.2 (t, 6 H, J=7.2 Hz), 4.3 (quartet, 4 H, J=7.2 Hz), 4.5 (s, 1 H), 5.3 (s, 1 H), 5.5 (s, 1 H), 7.3 (m, 5 H). M.W. 262 (MS). Found: C, 68.48; H, 6.62, Calcd. for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87%.

Product **4**: ^{1}HNMR δ 0.95 (t, 3 H, J=7.2 Hz), 1.3 (t, 3 H, J=7.1 Hz), 2.4 (s, 2 H), 3.9 (quartet, 2 H, J=7.1 Hz), 4.25 (quartet, 2 H, J=7.2 Hz), 7.1–7.4 (m, 5 H). M.W. 262 (MS). Found: C, 68.51; H, 6.73, Calcd. for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87%.

Product **5**: m.p. 93.5–94.5 (recryst. from CH_3OH). ^{1}HNMR δ 0.9 (t, 6 H, J=7.2 Hz), 1.2 (t, 6 H, J=7.0 Hz), 2.8 (s, 4 H), 3.9 (quartet, 4 H, J=7.0 Hz), 4.1 (quartet, 4 H, J=7.2 Hz), 7.0–7.3 (m, 10 H). M.W. 522 (MS). Found: C, 68.81; H, 6.56, Calcd. for $C_{30}H_{34}O_8$: C, 68.89; H, 6.51%.

From the nature of the products it appears likely that a free radical chain mechanism is involved. Since BNAH absorbs at 350 nm and **1** absorbs at 290 nm, only BNAH was excited under the experimental conditions. The mechanism is depicted in Scheme 1.

In this scheme, initial single electron transfer (SET) takes place from **2** in its excited state to **1**, the radical anion **6** formed rapidly dissociates to a neutral radical **7** and a bromide anion, and then **7** either abstracts a hydrogen to give an unsaturated ester or dimerizes to a dimer. Tanner and coworkers [13] have reported a SET-hydrogen atom abstraction chain mechanism for the reduction of α-haloketones by BNAH.

Evidence for a free radical mechanism was obtained from the spin-trapping experiment. When 2-nitroso-2-methylpropane was added to the reaction, ESR spectroscopy gave an ESR signal (Fig. 1) which was identified as that for the adduct with the structure shown in Fig. 1. This clearly shows that radical **7** was formed as an intermediate in this reaction.

Furthermore, when the 4-deuterated model BNAH-4,4-d_2 was used instead of BNAH as the reductant, the yield of **5** increased to 47% and that of **4** decreased to 11%, while the yield of **3** remained almost unchanged. Isotope analysis of the products by NMR and MS revealed that **4** contained deuterium whereas **3** did not. The results indicate that, while the trend of change of the yield of **4** and **5** is in conformity with a free radical mechanism due to the deuterium isotope effect, the fact that the yield of **3** remained almost unchanged and that it did not contain deuterium seems to suggest that some other mechanisms exist for the formation of **3**.

Quite interestingly, when magnesium perchlorate was added to the reaction, it brought about a marked change in

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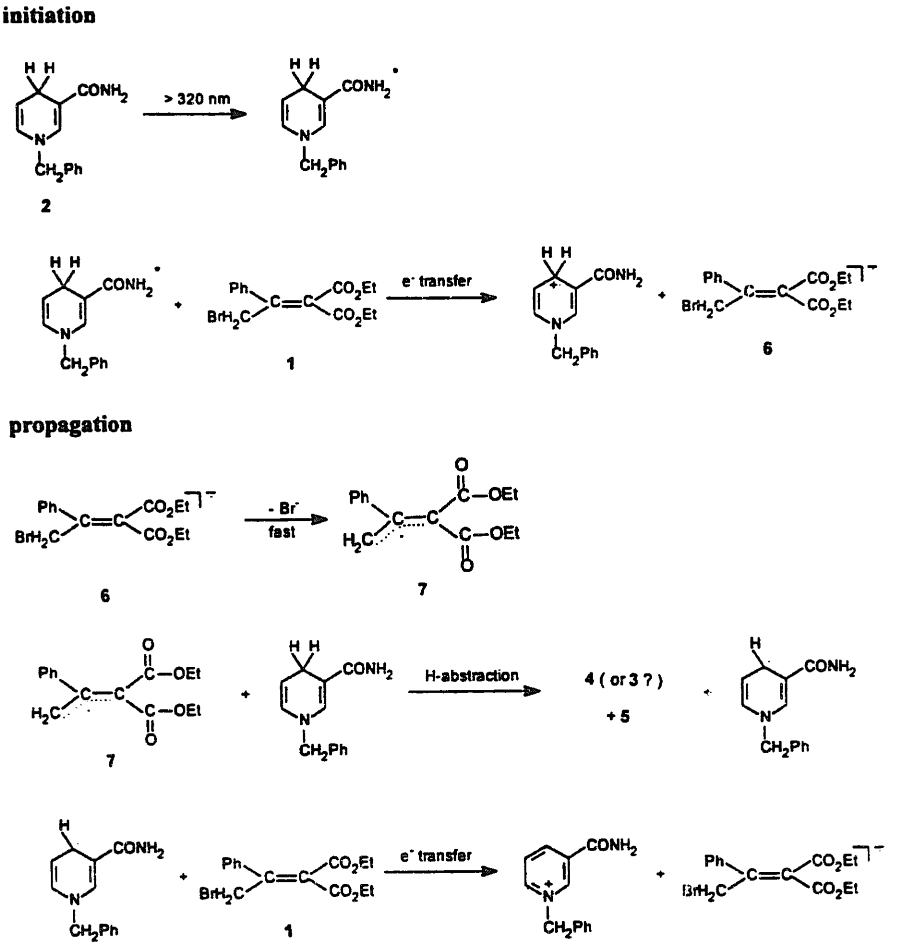
[1] Since 2-methyl-2-nitrosopropane produced under illumination ($\lambda > 320$ nm) an ESR signal of nitroxide radicals as impurities, the reaction mixture was irradiated for 3 min only and then the trapping reaction continued without irradiation because it was a chain reaction. No ESR signal for the trapped radical was observed without illumination.



Scheme 1.

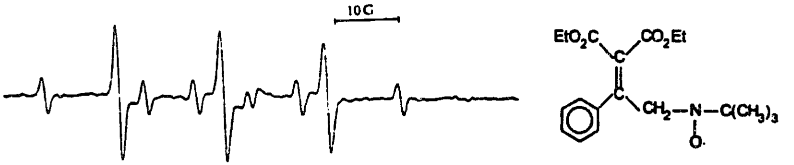


Fig. 1. ESR spectrum of the spin adduct obtained in the spin trapping experiment ($g = 2.0056$).

Table 1
Products and yields (%) from the reaction of **1** with BNAH and BNAH-4,4-d_2 in the presence and absence of Mg^{2+} ions

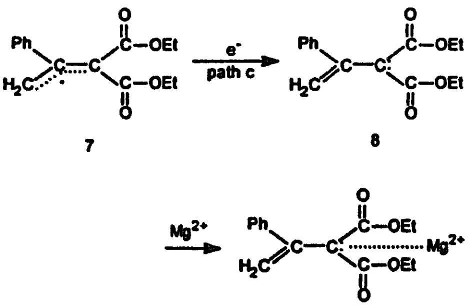
Product	BNAH		BNAH-4,4-d_2	
	With Mg^{2+}	Without Mg^{2+}	With Mg^{2+}	Without Mg^{2+}
3	87	24	85	22
4	trace	36	trace	15
5	trace	25	trace	47

the products formed, i.e. **3** was obtained as the sole predominant product while only traces of **4** and **5** were formed. The results described above are summarized in Table 1. The results were the same whether BNAH or BNAH-4,4-d_2 was used.

From Table 1 it is clearly seen that the Mg^{2+} ion has a catalytic effect on the formation of **3**. This indicates that a mechanism different from that for the formation of **4** and **5** must be involved.

The role of metal ions in the NADH model reduction of carbonyl compounds has been discussed in the literature [14]. It is known that the function of alcohol dehydrogenase (an NAD(P)H-dependent enzyme) requires the interaction of zinc ion which is suggested to coordinate with the carbonyl oxygen of the substrate and thereby to reduce the electron density at the carbonyl carbon [15]. Gase and Pandit [6] reported that the rate of reduction of (E)-2-, (E)-3- and (E)-4-cinnamoylpyridines by BNAH is fastest in the case of the 2-isomer, in which Mg^{2+} or Zn^{2+} ion is simultaneously complexed with the nitrogen and the oxygen sites, and they interpreted the results in terms of electrophilic catalysis of the reduction of these α,β-unsaturated ketones. Pac et al. [7] have demonstrated the marked effect of Mg^{2+} ion on the polarographic behavior of α,β-unsaturated esters so that prewaves appear at more positive potentials than $E_{1/2}^{\mathrm{red}}$ and increase in current with an increase in concentration of Mg^{2+} ion. They rationalize the results by postulating that the Mg^{2+} ion catalyzes the sequential two electron transfer from the reductant to the unsaturated ester.

In our experiment, the intermediate radical **7** is an allylic radical, one end of which is linked with two ethoxycarbonyl groups. Abstraction of a hydrogen (H) by the terminal γ-carbon atom to form an α,β-unsaturated carboxylic ester (**4**) (path **a**) is to be expected, while abstraction of a hydrogen by the α-carbon atom to form a β,γ-unsaturated ester (**3**) (path **b**) is unlikely to occur. On the other hand, **7** is able to undergo electron transfer with BNAH to produce a carbanion and, in this case, a carbanion (**8**) with the negative charge on the α-carbon atom will be favored because of the stabilizing effect of the two carbonyl groups attached to it. Protonation of this carbanion will give **3** (path **c**). When normal BNAH is used as the reductant, paths **a** and **c**, and dimerization of **7** occur simultaneously and so **3**, **4** and **5** are formed in comparable amounts. In the presence of Mg^{2+}, the rate of electron transfer to the radical intermediate (**7**) is greatly enhanced, owing to electrophilic catalysis by Mg^{2+}. Path **c** becomes the only favored path and so **3** is obtained as the exclusive product.



When the deuterated model BNAH-4,4-d_2 is used as the reductant, the same rationalization applies to the formation of **3**, **4** and **5** except that **3** contains no deuterium. This can be explained by the following two facts. One is that deuteron transfer has a large kinetic isotope effect [16,17]. Consequently, when the carbanion **8** is formed in the reaction of **7** with BNAH-4,4-d_2, it combines with a proton from the solvent during the work-up to give **3** rather than with a deuteron from the reductant. The other is that **3** may enolize especially when it is absorbed on silica gel in the process of purification. The enolization may result in exchange of α-proton (or deuteron) of the carboxylic ester with that of the solvent.

4. Conclusions

2-Bromo-1-phenylethylidenemalonic ester (**1**) reacts with BNAH (**2**) under illumination with $\lambda > 320$ nm via a SET-debromination chain mechanism. The intermediate radical **7** can react via three different pathways: (**a**) abstraction of a hydrogen from BNAH to give an α,β-unsaturated ester (**4**), (**b**) dimerization to a dimeric ester (**5**), and (**c**) second electron transfer from BNAH to give a carbanion with negative charge on the α-carbon atom, which protonates to form a β,γ-unsaturated ester (**3**). Magnesium ion has a remarkable catalytic effect on the sequence of two electron transfer (path **c**) so that **3** becomes the almost exclusive product. When BNAH-4,4-d_2 is used as the reductant, similar results obtain. In the latter case, **3** contains no deuterium, however. The mechanistic explanation is offered.

Acknowledgements

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