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A Study on the Reaction of 1-(3-Pyridyl)-2,2-di-substituted Ethylenes with 1-Benzyl-1,4-dihydronicotinamide

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The reaction of a series of 1-(3-pyridyl)-2,2-di-substituted ethylenes with 1-benzyl-1,4-dihydronicotinamide (BNAH) in deaerated acetonitrile produces the corresponding 1-(3-pyridyl)-2,2-di-substituted ethanes in contrast to benzylidenemalononitrile (BM) which does not react with BNAH under the same conditions.

Keywords 1-benzyl-1,4-dihydronicotinamide, 1-(3-pyridyl)-2,2-di-substituted ethylene, benzylidenemalononitrile, concerted hydride transfer

Introduction

Mechanism of the transfer of a formal hydride from the coenzyme nicotinamide adenine dinucleotide [NAD(P)H] to various substrates has drawn much attention because of its important role in many biochemical redox reactions.[1] One crucial yet controversial issue is whether the formal hydride transfer from NAD(P)H and its model compounds to the substrates occurs by one-step hydride transfer (polar mechanism) or multistep sequence of e^-–H^+–e^- or e^-–H· transfer (SET mechanism).[2]

Most research workers have focused their attention on the distinction between the polar mechanism and electron transfer mechanism and paid less attention to the relationship between them. Pross-Shaik valence-bond configuration mixing (VBCM) model[3] shows that polar and electron transfer pathways in organic chemistry are closely related processes and an intermediate pathway between these two mechanistic extremes is feasible. Verhoeven and co-workers[4] have studied the mechanism and transition state structure of hydride transfer reaction mediated by NAD(P)H models using the VBCM model and rationalized the general occurrence of concerted hydride transfer as the lowest energy pathway. Furthermore, the results also explain why the activation energy of such a concerted pathway is often linearly related to that of a hypothetical electron transfer process. Savéant and co-workers[5] have investigated the dynamics of proton transfer from cation radicals of NADH analogues with the conclusion that the deprotonation of these cation radicals in the ground states is better viewed as a concerted transfer of an electron and a hydrogen atom rather than a proton transfer in the strict sense. We[6] have investigated the reaction of 1,1-diphenyl-2,2-dinitroethylene with 1-benzyl-1,4-dihydronicotinamide (BNAH) in both deaerated and oxygen-saturated acetonitrile and obtained evidence indicating that the transition state for the reaction possesses partial diradical and partial covalent bonding character. Further study on the reaction of a series of 1,1-di-*p*-substituted phenyl-2,2-dinitroethylenes with BNAH has established the existence of a mechanistic spectrum of intermediate mechanism[7] consisting of different degrees of concertedness of electron transfer and hydrogen atom transfer.

In the previous study, we reported[8] that benzylidenemalononitrile (BM) did not react with BNAH in acetonitrile at room temperature in the dark but the reaction took place readily in the presence of magnesium perchlorate. The result was explained in terms of the coordination of Mg^{2+} to the two nitrile groups of BM which rendered the carbon-carbon double bond more reactive towards reduction.

In the present study, we wish to report the reaction of a series of 1-(3-pyridyl)-2,2-di-substituted ethylenes with BNAH. Since it is known[9] that the pyridyl group possesses stronger ability of electron withdrawing power than the phenyl group due to the electron-withdrawing inductive effect of the electronegative nitrogen atom, the result would reveal more insight on the mechanism for the formal hydride transfer from NADH models to activated ethylenic compounds. For this purpose, we have synthesized a series of 1-(3-pyridyl)-2,2-di-substituted ethylenes (**1**—**3**) and carried out their reaction with BNAH in acetonitrile.

Results and discussion

The results of the reactions of **1**—**3** with BNAH are

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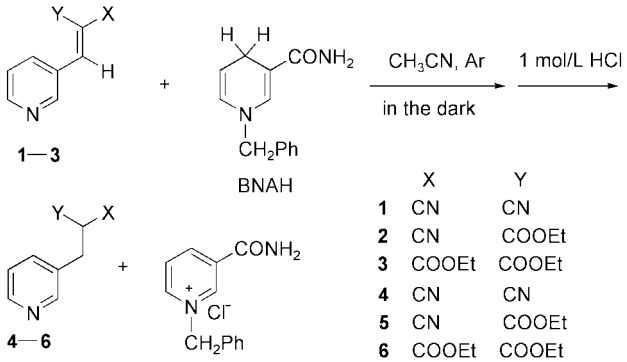
illustrated in Table 1.

Table 1 Reaction of **1**—**3** with BNAH



Substrate	E_{red}(vs. SCE)/V	Time	Yield[a]/%
1	−0.81	8	90
2	−0.88	12	85
3	−0.94	24	5 (without Mg^{2+}) 85 (with Mg^{2+})
BM[b]	−0.93	24	0 (without Mg^{2+}) 70 (with Mg^{2+})

[a] Isolated yield. [b] See reference 8.

The standard potential of BNAH was reported to be (786±8) mV vs. SCE.[5]

The results of the reaction of benzylidenemalononitrile (BM) with BNAH without and with Mg^{2+} are also included in Table 1.

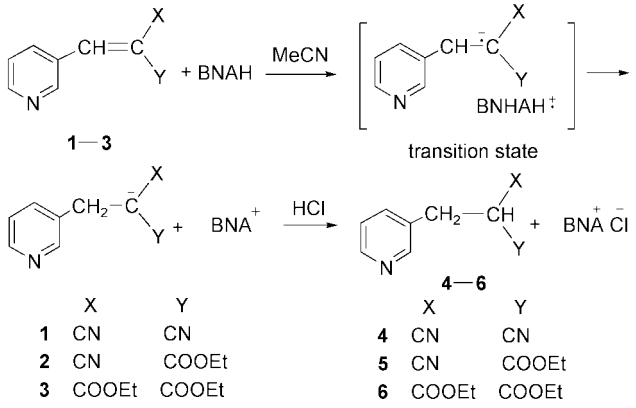
For comparison, the reactions of **1**—**3** with another reducing reagent sodium borohydride were carried out. When **1**—**3** were reduced with $NaBH_4$ in acetonitrile the corresponding reduced products **4**—**6** were obtained in over 90% yields.

The mechanism of the reaction of **1**—**3** with BNAH can be depicted as Scheme 1.

It is interesting to note from Table 1 that the reaction of **1** with BNAH gave 90% yield of the corresponding substituted ethane in contrast to the reaction of BM with BNAH, which produced nil under the same conditions. This must be attributed to the more electrophilic property of the 3-pyridyl group[9] according to the mechanism depicted in Scheme 1. It is also noted that while compound **2** reacts fairly readily with BNAH, compound **3** reacts much less readily than both **1** and **2**. The results can be rationalized by the fact that compound **3** contains two CO_2Et groups while **1** contains two CN groups and **2** contains one CN group and one CO_2Et group and the electron withdrawing power decreases in the order: 2CN > CN, CO_2Et > $2CO_2Et$.[10] However, the reaction of compound **3** with BNAH can be accelerated by the addition of magnesium perchlorate to the reaction mixture just the same as in the case of BM.[8] The role of Mg^{2+} ion in the NADH model mediated reduction of many compounds has been reported in the literature.[11]

Among the three differently substituted substrates **1**—**3**, the reactivity towards BNAH decreases in the following order: **1** (2CN) > **2** (1CN, 1CO_2Et) > **3** (2CO_2Et). This order is in consistence with the decrease of reduction potential of these compounds (Table 1).

Scheme 1



All of the results described above clearly show that electron withdrawing substituent groups facilitate the reduction of activated ethylenic compounds by BNAH models in accordance with concerted electron-hydrogen atom transfer mechanism.

Conclusion

In conclusion, the three 1-(3-pyridyl)-2,2-disubstituted ethylenes react with BNAH on account of the stronger electron withdrawing ability of the 3-pyridyl group than that of the phenyl group in BM which does not react with BNAH under the same conditions. The results lend support to the concerted electron-hydrogen atom transfer mechanism for the formal hydride transfer in BNAH mediated reductions of activated ethylenic compounds.

Experimental

Instruments and materials

^1H NMR spectra were recorded on a Bruker AM-300 NMR spectrometer in $CDCl_3$ with TMS as internal reference. ^{13}C NMR spectra were recorded on a Bruker AM-75 NMR spectrometer in $CDCl_3$ with TMS as internal reference. High-resolution mass spectra (HRMS) were determined on a Micromass GCT-MS mass spectrometer. Cyclic voltammetry was performed on an LK98BⅡ voltammograph in acetonitrile using SCE as reference electrode with tetraethylammonium perchlorate as supporting electrolyte. BNAH[12] and compounds **1**—**3**[13] were prepared according to the literature.

Electrochemical experiment

The electrode potential values of the reactants were determined by cyclic voltammetry at 50 $mV \cdot s^{-1}$ in acetonitrile containing 2 mmol/L **1**—**3** and 0.1 mol/L *n*-Bu_4NClO_4 at a glassy carbon electrode.

Reaction of 1—3 with BNAH

A flask containing **1**—**3** (1 mmol) and BNAH (1 mmol) was bubbled with dry argon for 10 min, another

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flask containing dry acetonitrile was bubbled with dry argon for 10 min, and a portion (10 mL) of the deaerated acetonitrile was taken and transferred to the former flask. The reaction vessel was then sealed and allowed to stand under argon at room temperature in the dark for corresponding time listed in Table 1. Hydrochloric acid (1 mol/L, 1 mL) was added, the mixture was extracted with chloroform and the combined extract dried with Na_2SO_4. After evaporation of the solvent, the residue was subjected to chromatography on a silica gel column with chloroform and petroleum ether as eluent. The pyridinium salt formed and unreacted BNAH were retained on the column. The products were then analyzed by ^{1}H NMR, ^{13}C NMR and HRMS.

Reaction of 1—3 with $NaBH_4$

A flask containing **1**—**3** (1 mmol) and $NaBH_4$ (1 mmol) was blown with dry argon for 10 min, another flask containing dry acetonitrile was bubbled with dry argon for 10 min, and a portion (10 mL) of the dry acetonitrile was taken and transferred to the former flask. The reaction vessel was then sealed and allowed to stand under argon at room temperature in the dark for 2 h. Hydrochloric acid (1 mol/L, 1 mL) was added, the mixture was extracted with chloroform and the combined extract dried with Na_2SO_4. After evaporation of the solvent, the residue was subjected to chromatography on a silica gel column with chloroform and petroleum ether as eluent. The same products **4**—**6** were obtained as described above with 90% yields.

2-[(Pyrid-3-yl)methyl] malononitrile (**4**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.36 (d, J=6.7 Hz, 2H), 4.05 (t, J=6.8 Hz, 1H), 7.40—7.45 (dd, J=7.8, 4.9Hz, 1H), 7.78 (d, J=7.9 Hz, 1H), 8.68 (d, J=5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.7 (CH), 33.8 (CH_2), 111.9 (CN), 124.1 (CH), 128.9 (CH), 137.0 (C), 150.3 (CH); HRMS (EI) calcd for $C_9H_7N_3$ 157.0640, found 157.0645.

Ethyl 2-cyano-3-(pyrid-3-yl)propanoate (**5**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.31 (t, J=8.6 Hz, 3H), 3.32 (d, J=6.6 Hz, 2H), 3.82 (t, J=6.6 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 7.52—7.56 (dd, J=7.8, 5.8Hz, 1H), 7.95 (d, J=7.9 Hz, 1H), 8.58 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.1 (CH_3), 32.3 (CH_2), 38.5 (CH), 63.8 (CH_2), 115.2 (CN), 125.6 (CH), 133.7 (CH), 140.2 (C), 147.0 (CH), 148.1 (CH), 164.5 (CO); HRMS (EI) calcd for $C_{11}H_{12}N_2O_2$ 204.0899, found 204.0898.

Diethyl 2-[(pyrid-3-yl)methyl] malonate (**6**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20—1.27 (m, 6H), 3.27 (d, J=7.6 Hz, 2H); 3.63 (t, J=7.6 Hz, 1H), 4.12—4.27 (m, 4H), 7.42—7.47 (dd, J=7.8, 5.8 Hz, 1H), 7.83 (d, J=7.8 Hz, 1H), 8.49 (d, J=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.0 (CH_3), 31.4 (CH_2), 52.7 (CH), 62.0 (CH_2), 125.2 (CH), 136.2 (CH), 139.9 (C), 145.9 (CH), 147.8 (CH), 167.9 (CO); HRMS (EI) calcd for $C_{13}H_{17}NO_4$ 251.1158, found 251.1161.

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