



A study on the reactions of NADH models with electron-deficient alkenes. A probe for the extreme of concerted electron-hydrogen atom transfer mechanism

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ABSTRACT

The reactions of 9-fluorenylidene malononitrile (FDCN) and 1,1-diphenyl-2,2-dicyanoethylene (DPCN) with Hantzsch ester (HEH), *N*-methyl Hantzsch ester (Me-HEH), and 1-benzyl-1,4-dihydronicotinamide (BNAH) in oxygen-saturated acetonitrile have been studied. The aerobic reactions with HEH give solely reduction products. However, reactions with Me-HEH and BNAH not only result in reduction products, but also give varying amounts of oxidation products. The amount of oxidation product appears to be related to the electronic character and bulkiness of reactants. We propose that all these reactions follow a general mechanism of concerted electron-hydrogen atom transfer mechanism. If the electron-transfer complex is very tight, only 'concerted hydride transfer reaction' occurs. However, if the electron-transfer complex is not so tight, oxygen can capture the radicaloid intermediate to result in oxidation products.

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In recent years, the idea that hydride transfer from coenzyme NADH models takes place through a concerted electron-hydrogen atom transfer mechanism (concerted hydride transfer) has gained increasing support from many investigators.^{1–3} Verhoeven et al.⁴ have applied the valence-bond configuration mixing (VBCM) model⁵ to the study of mechanism and transition state structure of hydride transfer reactions mediated by NAD(P)H models and rationalized the results with the notion that the general occurrence of concerted hydride transfer as the lowest energy reaction pathway, which also explains why the activation energy of such a concerted pathway is often linearly related to that of a hypothetical single electron-transfer process.

Savéant et al.⁶ have studied the dynamics of proton transfer from the cation radicals of NADH analogues and found that the homolytic cleavage of the [•]C–H bond appears to be the dominant factor governing the dynamics of proton transfer in the series of NADH cation radicals studied and suggested that the proton transfer from the cation radical is better viewed as a concerted electron-hydrogen atom transfer rather than a stricto sensu proton transfer.

The investigations of our laboratory on the reactions of NADH models with activated ethylenic compounds also provided evidence for concerted electron-hydrogen atom transfer mechanism for equivalent hydride transfer. Thus, in the reactions of 1,1-di-*p*-substituted phenyl-2,2-dinitroethylenes with 1-benzyl-1,4-dihydronicotinamide (BNAH) to give the corresponding di-*p*-

substituted phenyl ethanes, kinetic studies showed that the relative rates of reactions bear a good linear relationship with Hammett σ constants for the *p*-substituent groups.⁷ The same reactions carried out in oxygen-saturated acetonitrile produced the corresponding di-*p*-substituted ethanes and di-*p*-substituted aryl ketones in variable ratios determined by the nature of the electronic character of the *p*-substituent groups.⁸ The results are consistent with the conception that, due to the electronic and steric effect of the substituent groups on the ethylenic linkage, electron transfer and hydrogen atom transfer from BNAH to the substrate molecule do not take place synchronously, electron transfer has progressed farther than hydrogen atom transfer, so that the transition state possesses partial diradical and partial covalent bonding character, which bifurcates in the presence of oxygen into two pathways leading to the formation of the corresponding 1,1-di-*p*-substituted aryl-2,2-dinitroethane and di-*p*-substituted aryl ketone.⁹

Recently, Hantzsch ester (HEH) has been widely used as reducing agent for organocatalytic hydrogenation of α,β -unsaturated aldehydes,^{10a–e} α,β -unsaturated ketones,^{10f,g} and imines.^{10h–j} We also found that *N*-methyl Hantzsch ester (Me-HEH) can convert α,β -epoxy ketones to β -hydroxy ketones.^{10k} The reaction mediated by Me-HEH appears to be electron-transfer mechanism,^{10k} while the reaction mediated by HEH is generally considered as direct hydride transfer.¹¹ It appears, therefore, the mechanism may differ with different substrates and more investigation is needed.

Recently, we studied the reactions of HEH and Me-HEH with FDCN and DPCN in deaerated acetonitrile and oxygen-saturated acetonitrile, respectively. The objective of the research is twofold:

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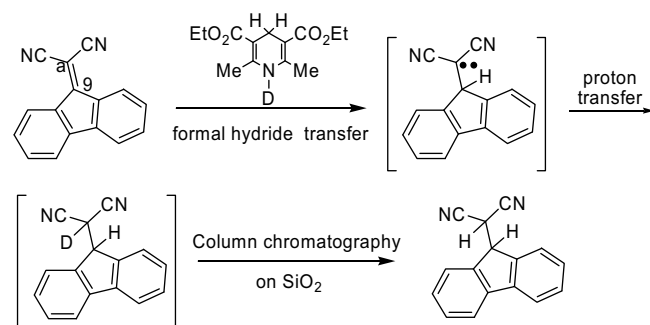
firstly, to find the extreme case of concerted electron-hydrogen atom transfer, which is equivalent to direct hydride transfer, and secondly, to elucidate the substituent effect upon the mechanism. For comparison, the reaction of BNAH with FDCN and DPCN is also studied to ascertain the scope and generality of the reaction mechanism (Fig. 1).

FDCN reacted with HEH in dry deaerated acetonitrile at 30 °C under Argon in the dark for 6 h to give 9-fluorenylmalononitrile (FDCNH) in 91% yield (Table 1, entry 1). In this reaction no quenching agent such as hydrochloric acid is added because the intermediate Hantzsch ester radical cation is a strong acid,¹² which provides the proton for quenching the reaction. The addition of *m*-dinitrobenzene to the reaction showed no inhibiting effect upon the reaction.

Isotope tracing experiment using *N*-deuterated Hantzsch ester shows that deuterium goes to the α -position of FDCNH and the result is in consistence with the mechanism depicted in Scheme 1. The reactions of FDCN with Me-HEH and BNAH were carried out in dry deaerated acetonitrile under argon for appropriate time and then quenched with acetic acid (Table 1, entries 2 and 3). Addition of *m*-dinitrobenzene showed no appreciable effect upon the reaction of FDCN with Me-HEH but showed remarkable baffling effect to the reaction of FDCN with BNAH.

The reactions of DPCN with the three models needed higher reaction temperatures, longer reaction time and the yields were relatively lower than that of the reactions of FDCN (Table 1, entries 4–6).

Table 2 summarizes the results of reactions of FDCN and DPCN with NADH models in oxygen-saturated acetonitrile. The reaction of FDCN with HEH in oxygen-saturated acetonitrile gave the same products as that in deaerated acetonitrile (Table 2, entry 1). No

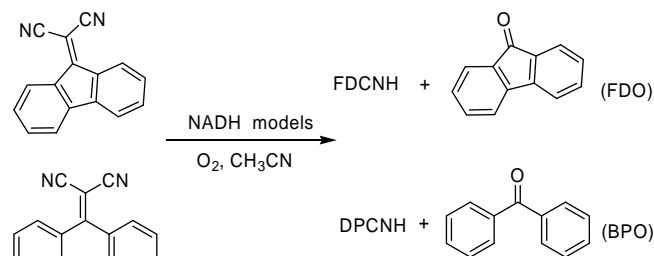


Scheme 1. Isotope tracing experiment.

oxidation product was obtained. However, in the reaction of FDCN with Me-HEH in oxygen-saturated acetonitrile, the products obtained consisted of not only FDCNH (78%) but also small amounts of 9-fluorenone (FDO, 8.3%) (Table 2, entry 2). TLC tests indicated that FDO was formed gradually in the progress of the reaction and reached the maximum and then ceased to increase. When BNAH was used in the reaction with FDCN in oxygen-saturated acetonitrile, FDCNH was surprisingly the minor product (6%) and

Table 2

Reaction of FDCN and DPCN with NADH models in oxygen-saturated acetonitrile^a



Entry	Reaction	T (°C)	Time (h)	Product/yield ^b (%)
1	FDCN + HEH	30	12	FDCNH (90), FDO (0)
2	FDCN + Me-HEH	30	12	FDCNH (78), FDO (8.3)
3	FDCN + BNAH	30	12	FDCNH (6), FDO (76)
4	DPCN + HEH	40	24	FDCNH (30), BPO (0)
5	DPCN + Me-HEH	60	24	DPCNH (46), BPO (2)
6	DPCN + BNAH	40	24	DPCNH (15), BPO (11)

^a General conditions: FDCN or DPCN (0.1 mmol), NADH models (0.15 mmol), CH₃CN (15 mL).

^b Isolated yield based on ethylenic substrates.

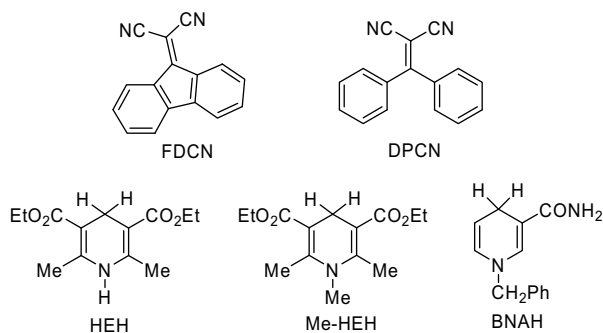
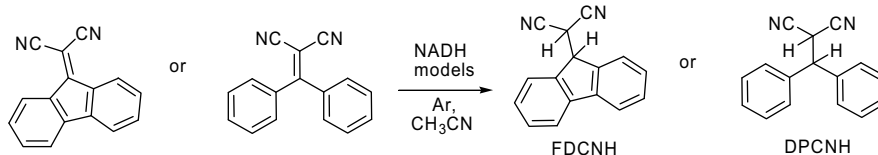


Figure 1.

Table 1

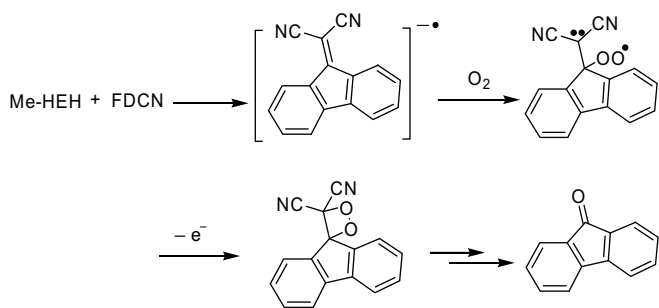
Reactions of FDCN and DPCN with NADH models in deaerated acetonitrile^a



Entry	Reaction	T (°C)	Time (h)	Product/yield ^b (%)
1	FDCN + HEH	30	6	FDCNH (91)
2	FDCN + Me-HEH	30	12	FDCNH (80)
3	FDCN + BNAH	30	6	FDCNH (85)
4	DPCN + HEH	40	24	DPCNH (30)
5	DPCN + Me-HEH	60	24	DPCNH (40)
6	DPCN + BNAH	40	24	DPCNH (35)

^a General conditions: FDCN or DPCN (0.1 mmol), NADH models (0.15 mmol), CH₃CN (15 mL).

^b Isolated yield based on ethylenic substrates.



Scheme 2. Mechanism of the formation of FDO.

FDO became the major product (76%) (Table 2, entry 3). The reaction of DPCN with HEH still gave only the reduction product (Table 2, entry 4). Benzophenone (BPO) was isolated in the reactions of DPCN with Me-HEH and BNAH in oxygen-saturated acetonitrile with the yields of 2% and 11%, respectively (Table 2, entries 4 and 5). The ratios of BPO versus DPCNH decreased when compared with that of FDO versus FDCNH.

With reference to the literature¹³ and our previous report,¹⁴ the formation of FDO and BPO is attributed to the reactions of oxygen with the anionic radicaloid species in the transition states formed via electron transfer from the NADH models to FDCN and DPCN (Scheme 2).

Table 3 gives the redox potentials of the reactants. A simple calculation of the energy for an electron transfer would be prohibitive for the reaction since the easiest one would be between BNAH and FDCN, endothermic by about 30.2 kcal/mol ($\Delta E = 23.02(E_{\text{red}} - E_{\text{ox}})$ kcal/mol). However, such an electron transfer would be possible in a radical cation/radical anion complex. Charge transfer complexes between NADH models and alkenes have been well realized both in enzyme active site¹⁵ and in solution.¹⁶

The tightness of the electron-transfer complex is dependent upon the redox potentials of the reactants as well as steric effect. Large endothermicity of the electron-transfer reaction and smaller steric effect should result in a tighter complex while smaller endothermicity of the electron-transfer reaction and larger steric effect should be associated with a looser complex. Thus, HEH, which is planar and has the highest oxidation potential, should correspond to a very tight complex. In addition, the bond dissociation energy for C₄-H bond of HEH is supposed to be of a relatively low value,¹⁷ the H-atom transfer should be easier to take place. It appears, therefore, the reaction takes place via a completely concerted electron-hydrogen atom transfer mechanism and there is no feasibility for oxygen to react with the transition state and no FDO is formed. On the other hand, in the case of Me-HEH, because of the steric effect of the N-Me group, the transition state complex between Me-HEH and FDCN is not so 'tight' as that between HEH and FDCN so that it is feasible for oxygen molecule to approach and react with the anionic radicaloid center to form a peroxidic intermediate, which eventually transforms to FDO (Scheme 2).

BNAH has the lowest oxidation potential. It should form loose electron-transfer complex. It is thus not surprising that when FDCN reacts with BNAH in oxygen-saturated acetonitrile, the products

obtained consist of FDCNH (6%) and FDO (76%) with the latter as the predominant product.

From the above analysis, it is seen that there is a mechanistic extreme in the concerted electron-hydrogen atom transfer mechanism, which is equivalent to direct hydride transfer.

Fukuzumi and co-workers¹⁸ have recently reported the detailed investigation on the borderline between one-step hydride transfer and multistep electron transfer-proton transfer or electron-proton-electron transfer of NADH analogues in some specific reaction systems.

In the reaction of DPCN with Me-HEH in oxygen-saturated acetonitrile, owing to the fact that the two phenyl groups are not coplanar with C-C double bond and there is a methyl group on the NADH model, the steric effect renders the reaction of oxygen with the transition state feasible and BPO is obtained as the oxidation product in addition to the reduction product.

Supporting evidence for concerted electron-hydrogen atom transfer is also provided by the fact that the reaction of 1,1-di-*p*-methoxyphenyl-2,2-dinitroethylene with BNAH to give high yield (>90%) of 1,1-di-*p*-methoxyphenyl-2,2-dinitroethane, whereas 1,1-di-*o*-methoxyphenyl-2,2-dinitroethylene does not react with BNAH even in the presence of magnesium perchlorate or upon irradiation with light, although it can be readily reduced to the corresponding substituted ethane with sodium borohydride.¹⁹ This retardation effect of the ortho substituent clearly indicates concerted electron-hydrogen atom transfer mechanism.²⁰

In summary, by comparison of the reactions of HEH, Me-HEH, and BNAH with FDCN and DPCN in deaerated acetonitrile²¹ and oxygen-saturated acetonitrile²², it is reasonable to conclude that all these reactions take place via an electron-hydrogen atom transfer mechanism and the difference exists only in the degree of concertedness. The reaction of FDCN with HEH appears to represent the extreme case of concerted hydride transfer.

Acknowledgments

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Table 3
Electrode potentials (V, vs Ag/AgCl) of NADH models, FDCN, and DPCN

	FDCN	DPCN	HEH	Me-HEH	BNAH
E_{ox}			1.01	0.93	0.63
E_{red}	-0.68	-0.83			

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 21. *General procedure for the reduction of activated alkenes by NADH models:* A mixture of FDCN (0.1 mmol) and HEH (0.15 mmol) in 15 ml deaerated acetonitrile was left in the dark at 30 °C for 6 h. The reaction mixture was evaporated under reduced pressure to dryness and the residue was subjected to column chromatography on silica gel with petroleum ether–ethyl acetate (10:1, v:v) as eluant to give FDCNH as a white solid. Yield: 21 mg (91%). Mp 164–166 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.81 (2H, d, *J* = 7.5 Hz), 7.76 (2H, d, *J* = 7.5 Hz), 7.51 (2H, t, *J* = 7.5 Hz), 7.41 (2H, t, *J* = 7.5 Hz), 4.42 (1H, d, *J* = 5.3 Hz), 4.23 (1H, d, *J* = 5.3 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 141.47, 139.75, 129.76, 128.16, 124.73, 120.83, 111.65, 46.02, 27.72. EIMS: *m/z* (rel. intensity) 230 (M⁺, 19), 165 (100).
 22. *General procedure for the reaction of activated alkenes with NADH models in oxygen-saturated acetonitrile:* Acetonitrile (15 ml) was bubbled with dry oxygen for 10 min. FDCN (0.1 mmol) and Me-HEH (0.15 mmol) were added and the reaction vessel was sealed. After reaction at 30 °C for 12 h in the dark under positive pressure of oxygen, the reaction mixture was quenched with acetic acid (1 M, 0.5 ml). The solvent was evaporated under reduced pressure and the residue was worked up by column chromatography on silica gel with petroleum ether–ethyl acetate (10:1, v:v) as eluant to give the products FDO (1.5 mg, 8.3%) and FDCNH (17.9 mg, 78%). FDO: yellow solid. Mp 82–83 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (2H, d, *J* = 7.3 Hz), 7.52 (2H, d, *J* = 7.3 Hz), 7.48 (2H, t, *J* = 7.3 Hz), 7.30 (2H, t, *J* = 7.3 Hz). EIMS: *m/z* (rel. intensity) 180 (M⁺, 100), 165 (68).