Reduction by a Model of NAD(P)H. 35. Spectroscopic Detection of Charge-transfer Intermediate

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4,4-Disubstituted 1,4-dihydropyridine derivatives are employed as models of NAD(P)H. Electronic and ESR spectroscopies have proved that these models form charge-transfer complexes with certain substrates, which supports a mechanism of the reduction with 1,4-dihydronicotinamide derivatives to be initiated by initial electron-transfer.

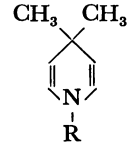
It has been proposed that the reduction of an unsaturated compound with an NAD(P)H-model involves at least one intermediate.[1-3] The nature of the intermediate has been discussed, but direct evidence has scarcely reported.[2,4,5]

Recently, we reported that results from the studies on kinetics and isotope effects for the reduction of a series of substituted and unsubstituted α,α,α-trifluoroacetophenone with 1-propyl-1,4-dihydronicotinamide revealed the importance of initial electron-transfer.[3] Stereochemistry of the reduction with a chiral model compound also supported the proposed mechanism.[6] However, since the intermediate undergoes further reaction spontaneously, it is not easy to detect it. Only when the intermediate becomes thermodynamically more stable than the reactant system, the detection has been succeeded.[2,4,5]

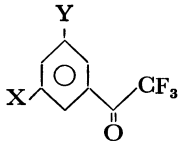
In order to obtain direct evidence for an unstable intermediate, we studied electronic and ESR spectroscopies by the aid of model compounds that have no C_4-hydrogen.

Results

1-Propyl-4,4-dimethyl-1,4-dihydropyridine (**1a**) and 1-phenyl-4,4-dimethyl-1,4-dihydropyridine (**1b**) were employed as reductants.



1a: R=C_3H_7
1b: R=C_6H_5



2a: X=H, Y=Br
2b: X=H, Y=CF_3
2c: X=H, Y=NO_2
2d: X=CF_3, Y=NO_2

Electronic Spectra. To test the formation of a stable charge-transfer (CT) complex with **1a** or **1b**, strongly electron-demanding substrates such as TCNQ, *N*-methylacridinium iodide, and 1,3,5-trinitrobenzene were used for the spectroscopy. Note that these substrates are known to form stable intermediates with an ordinary NAD(P)H-model which has a C_4-hydrogen.[2,3,7,8] When, TCNQ was mixed with **1a** in anhydrous acetonitrile at 50 °C, the solution turned green and exhibited a spectrum with absorption maxima at 746, 764, 825, and 846 nm as shown in Fig. 1. The complexation constant was measured to be 116 M^{-1}. The spectrum is identical to those reported previously.[9,10] 1,3,5-Trinitrobenzene (Fig. 2)[11] and *N*-methylacridinium iodide (Fig. 3)[2] also showed CT-bands when they were mixed with **1b** in acetonitrile.

m-Bromo- (**2a**), *m*-trifluoromethyl- (**2b**), *m*-nitro- (**2c**), and *m*-trifluoromethyl-*m'*-nitro- (**2d**) α,α,α-trifluoroacetophenones were, then, subjected to the spectroscopy. Kinetics and other evidence have predicted that the intermediates formed from these substrates are thermodynamically less stable than their corresponding reactant systems.[3] Yet, their mixtures with **1a** in acetonitrile clearly showed new absorptions with maxima at 367, 369, 371, and 374 nm for **2a**, **2b**, **2c**, and **2d**, respectively, as shown in Fig. 4. The

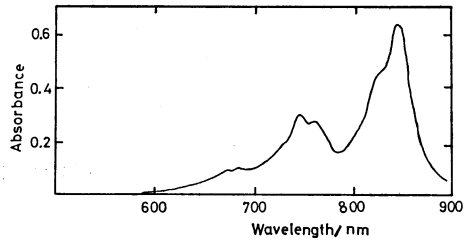


Fig. 1. Electronic spectrum of anion radical of TCNQ.

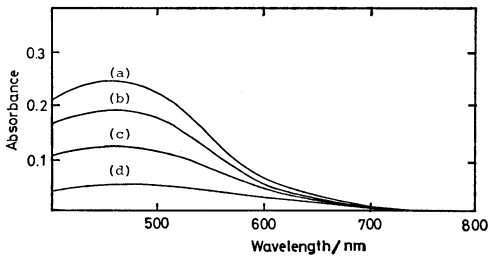


Fig. 2. CT spectra of 1,3,5-trinitrobenzene and 1-phenyl-4,4-dimethyl-1,4-dihydropyridine; (a) [TNB] $=3.56\times10^{-2}$ M, [**1b**]$=3.15\times10^{-2}$ M; (b) [TNB]$=3.67\times10^{-2}$ M, [**1b**]$=2.32\times10^{-2}$ M; (c) [TNB]$=3.79\times10^{-2}$ M, [**1b**]$=1.44\times10^{-2}$ M; (d) [TNB]$=3.91\times10^{-2}$ M, [**1b**]$=0.495\times10^{-2}$ M.

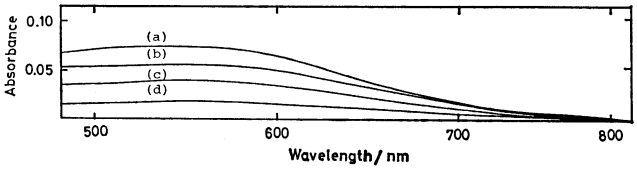


Fig. 3. CT spectra of *N*-methylacridinium iodide and 1-phenyl-4,4-dimethyl-1,4-dihydropyridine; (a) [AI]$=1.20\times10^{-2}$ M, [**1b**]$=6.35\times10^{-2}$ M; (b) [AI]$=1.30\times10^{-2}$ M, [**1b**]$=4.31\times10^{-2}$ M; (c) [AI]$=1.38\times10^{-2}$ M, [**1b**]$=2.74\times10^{-2}$ M; (d) [AI]$=1.47\times10^{-2}$ M, [**1b**]$=0.973\times10^{-2}$ M.

new absorptions satisfied well-known criteria for CT-complexation in solution.[12]

ESR Spectra. A mixture of TCNQ with **1a** in tetrahydrofuran at room temperature (about 25 °C) gave well-resolved ESR signals that were attributable to the signals from anion radical of TCNQ.[10,13] The spectrum is shown in Fig. 5. On the other hand, substrates **2a**—**d** did not give signals under the same condition. However, when magnesium perchlorate was added to the system, broad but distinct signals were recorded. A spectrum from **2d** is shown in Fig. 6 as a representative. The spectrum with $g=2.003$ is characterized by a large width of about 100 G, which indicates that the splitting due to fluorine atoms is involved in the spectrum. The recorded spectrum is identical to that observed from the system of **2d** and sodium metal (Fig. 6b). The signal width is identical to that reported for anion radical of α,α,α-trifluoroacetophenone.[14]

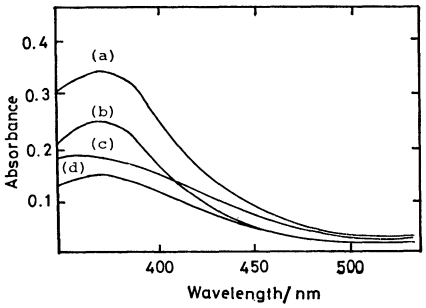


Fig. 4. CT spectra of substituted α,α,α-trifluoroacetophenones and 1-propyl-4,4-dimethyl-1,4-dihydropyridine; (a) [**2d**]$=1.39\times10^{-2}$ M, [**1a**]$=5.58\times10^{-2}$ M; (b) [**2c**]$=1.23\times10^{-2}$ M, [**1a**]$=1.98\times10^{-2}$ M; (c) [**2a**]$=4.57\times10^{-2}$ M, [**1a**]$=6.42\times10^{-2}$ M; (d) [**2b**]$=4.71\times10^{-2}$ M, [**1a**]$=3.84\times10^{-2}$ M.

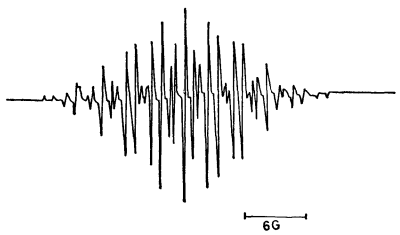


Fig. 5. ESR spectrum of anion radical of TCNQ.

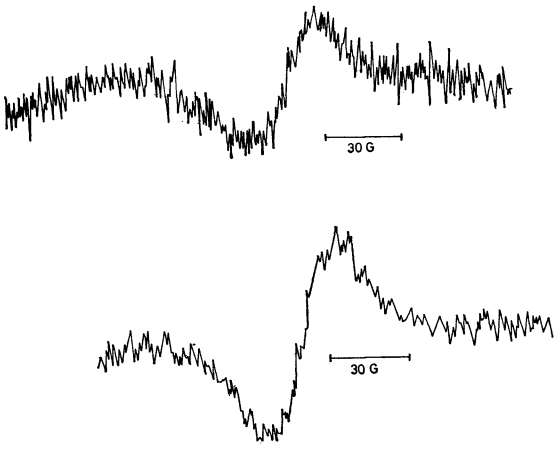


Fig. 6. ESR spectra from mixtures of *m*-trifluoromethyl-*m'*-nitro-α,α,α-trifluoroacetophenone and (a) 1-propyl-4,4-dimethyl-1,4-dihydropyridine and (b) sodium metal.

Discussion

Thus, both electronic and ESR spectroscopies have proved that 1,4-dihydropyridine can transfer an electron onto certain substrate forming a CT-complex. However, there still remains a question whether the detected intermediate is abortive or real. In this connection, it should be noted that the substrates **2a**—**c** are those the reduction of which is catalyzed by magnesium ion.[3] If magnesium ion increased the concentration of abortive CT-complex to exhibit an ESR signal, or if the concentration of reacting substrate were decreased by the addition of magnesium ion, the reduction in the presence of magnesium ion must be slower than that in its absence. The fact that the increase in reduction rate corresponds with the increase in concentration of CT-complex reveals that the CT-complex is not an abortive species but is a real intermediate of the reduction.

In conclusion, we have succeeded to prove that the initial step of the reduction with an NAD(P)H-model is an electron-transfer process.

Experimental

Materials. Acetonitrile was distilled three times on phosphorous pentoxide. Tetrahydrofuran was distilled and dried over sidium, then dried over alloy of potassium and sodium under reduced pressure. TCNQ and 1,3,5-trinitrobenzene were purchased from Nakarai Chem. Co. and purified by recrystallization. *N*-Methylacridinium iodide (mp 87 °C),[12] *m*-bromo-α,α,α-trifluoroacetophenone (bp 78 °C/15 mmHg) (**2a**),[15] *m*-trifluoromethyl-α,α,α-trifluoroacetophenone (bp 150 °C/760 mmHg) (**2b**),[3] *m*-nitro-α,α,α-trifluoroacetophenone (mp 54 °C) (**2c**),[15] and *m*-trifluoromethyl-*m'*-nitro-α,α,α-trifluoroacetophenone (bp 90 °C/8 mm Hg) (**2d**)[3] were prepared according to literature procedures. 1-Propyl-4,4-dimethyl-1,4-dihydropyridine (bp 72 °C/47 mmHg) (**1a**)[16] and 1-phenyl-4,4-dimethyl-1,4-dihydropyridine (mp 36 °C) (**1b**)[17] were also synthesized according to literature procedures. All materials gave satisfactory results from elemental analyses and spectroscopies.

Visible Spectra. Acetonitrile was flushed with dry argon prior to use. A solution of a substrate in acetonitrile was prepared and placed in a cell (1 cm) equipped with a silicone-rubber stopper, then the solution of a model compound in acetonitrile was injected into this solution. Visible spectra was obtained with Union Giken SM-401 spectrometer, the cell-compartment of which was filled with dry argon and kept at 50.0±0.1 °C.

The measurement of association (complexation) constant of TCNQ with **1a** was carried out by the procedure described below. The concentration of **1a** was kept at 2×10^{-4} M and the concentration of TCNQ was changed from 1.58×10^{-3} to 6.32×10^{-3} M. The change in the intensity at 746 nm was measured. The slope of the double reciprocal plot of the intensity and the concentration of TCNQ gave a linear line.

Spectra of the other substrates were obtained with the

Table 1. Concentrations of reagents for the observation of charge-transfer spectra

Substrate	Concn/10^{-2} M	Model	Concn/10^{-2} M
1,3,5-Trinitrobenzene	3.50—3.90	**1b**	0.5—3.2
N-Methyl acridinium iodie	1.25—1.50	**1b**	1.0—6.3
2a	4.40—5.50	**1a**	1.0—8.0
2b	4.40—4.90	**1a**	1.0—8.0
2c	1.21—1.25	**1a**	1.0—3.0
2d	1.39—1.48	**1a**	2.0—5.6

concentrations listed in Table 1.

ESR Spectra. Appropriate amounts of a substrate and **1** were placed in a sample tube and desired amount of the purified dry tetrahydrofuran was brought into the tube in a vacuum. The spectra were obtained on a JEOL-JMS-ME-3X spectrometer at room temperature or below.

Correlation of Physical Units. Physical units used in this report are correlated with SI-unit by the following relationship.

1 M=1 mol dm^{-3}, t/°C=T/K−273.15, p mmHg=13.5951 ×980.665×10^{-2} p Pa.

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