

Structural Studies on Cyclic Compounds. Substituent Effects on the Reducing Ability of Dihydropyridines

Kwanghee Koh Park*, Gyeong Un Moon, Ki-Sung Kwon

Department of Chemistry, Chungnam National University, Daejeon 300-31. Received February 11, 1987

The reaction between 1-benzyl-3-carbamoyl-1,4-dihydropyridine (BNAH) **1** and various 1-arylpyridinium salts **2**, and the reaction between 1-(4-methylphenyl)-1,4-dihydropyridine **4b** and 1-aryl-3-carbamoylpyridinium (1-arylnicotinamide) salts **5** were carried out. The extents of reaction in equilibrium were estimated by nmr integration data. The equilibrium constants for the reactions, K , and the standard Gibbs free energy changes for the reduction of the pyridinium salts to the corresponding 1,4-dihydropyridines ΔG° were evaluated. The Hammett plot of $\log K$ for the reaction between **1** and **2**, and ΔG° against σ_p of the substituents in 1-aryl moiety shows linear correlation with the reaction constant ρ of 9.4 (for $\log K$ vs σ_p) and -54.5 KJ/mole (for ΔG° vs σ_p). It was found that 1-aryl-1,4-dihydropyridines have much higher reducing power than the corresponding 1-aryl-1,4-dihydronicotinamides, and the power is affected greatly by the electron-withdrawing ability of the substituents in aryl group. The reactions were utilized for preparation of 1,4-dihydropyridines bearing highly electron-withdrawing groups such as 4-nitrophenyl and 2,4-dinitrophenyl, which could not be obtained by conventional dithionite reduction of the corresponding pyridinium salts due to the base-labile nature of the salts.

Introduction

The fact that a "hydrogen-transferring coenzyme" is a reduced form of nicotinamide, 3-carbamoylpyridine, derivative has stimulated work on model of NAD(P)H coenzyme.¹ Thus considerable efforts have been made in synthesizing NAD(P)H mimics, exploring the reactions and mechanisms involving the compounds, and utilizing them in a variety of synthetic reactions.^{2,4}

Reduction by NAD(P)H model compounds was first reported by Westheimer for reduction of Malachite Green by 1-benzyl-1,4-dihydronicotinamide (BNAH) in 1955.⁵ Thereafter numerous works on reduction of unsaturated functionalities by 1,4-dihydropyridines have been followed. These include reduction of ketones and aldehydes to alcohols,⁶ and imines to amines.⁷ The net chemical change in the reduction processes is the transfer of hydride ion from 1,4-dihydropyridines to substrates. Similarly, the transfer of other nucleophiles from 4-substituted 1,4-dihydropyridines was synthetically utilized.⁸ Also, recycling of NAD(P)H by reduction of NAD(P)⁺ with dihydropyridines in NAD(P)H dependent enzyme-catalyzed organic synthesis was investigated.⁹

Afore-mentioned applications of dihydropyridines in organic synthesis are based on the reducing ability of the compounds. Though 1,4-dihydropyridines can reduce various organic functional groups, the reduction by them are applicable only to activated unsaturated groups, and 1-alkyl-1,4-dihydronicotinamides were mainly used as NAD(P)H model. Little work has been reported on the correlation between structure and reducing power of dihydropyridines. Therefore information on the factors governing the reducing power of dihydropyridines is clearly desirable. In this paper, we report the results of reactions between various pairs of 1,4-dihydropyridines and pyridinium salts, which show that the reducing power of 1,4-dihydropyridines is greatly affected by the substituent at 1- or 3-position.

Experimental

¹H-nmr spectra were taken with a Varian Model EM-

360A or FT-80A spectrometer, and chemical shifts were expressed as units relative to TMS (in CDCl₃) or DSS (in D₂O) as an internal standard.

1-arylpyridinium **2** and 1-aryl-3-carbamoylpyridinium (nicotinamide) salts **5** were prepared by the procedures described elsewhere.¹⁰ 1-benzyl-3-carbamoylpyridinium chloride **3** was obtained from the reaction of nicotinamide with benzyl chloride. 1,4-dihydropyridines **1**, **4** and **6** except 1-(2,4-dinitrophenyl)-1,4-dihydropyridine **4f** and 1-(4-nitrophenyl)-3-carbamoyl-1,4-dihydropyridine **6e**, 1-(2,4-dinitrophenyl)-3-carbamoyl-1,4-dihydropyridine **6f**, were made by reducing the corresponding pyridinium salts with sodium dithionite.¹¹ The compounds **4f**, **6e** and **6f** were prepared by reactions of Eqs. 1 and 2 applying the procedures in the following.

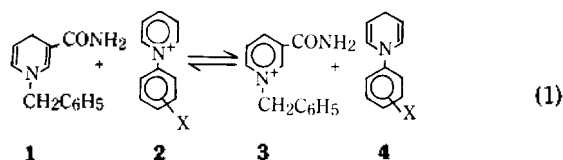
Reactions between BNAH 1 and 1-arylpyridinium chlorides 2(Eq. 1). The mixtures of 0.214 gr (1 mmole) of BNAH **1** and 1 mmole of 1-arylpyridinium chloride **2a-f** in 40 ml of absolute ethanol were stirred at 30°C under nitrogen atmosphere for 3 or 6 hours. For dark condition, the reaction vessel was wrapped with aluminium foil. The reaction mixtures were concentrated by a rotary evaporator under reduced pressure. The residue was taken up in 5-10 ml of water and the undissolved solid was filtered. The water-insoluble solid was dissolved in CDCl₃ and its nmr spectrum was taken. The filtrate was concentrated under reduced pressure to obtain water-soluble pyridinium salts, and its nmr spectrum was taken in D₂O.

Reactions between 1-(4-methylphenyl)-1,4-dihydropyridine 4b and 1-aryl-(3-carbamoylpyridinium chlorides 5(Eq. 2). The mixtures of 0.171 gr (1 mmole) of **4b** and 1 mmole of 1-aryl-3-carbamoylpyridinium chloride **5a-f** in 40 ml of 90% ethanol were reacted and worked up as described above for reactions of Eq. 1. The nmr spectra of the water-insoluble components (dihydropyridines) were taken in the mixture of CDCl₃ and DMSO-d₆.

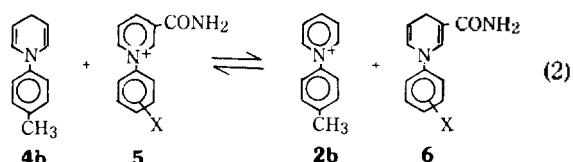
Results and Discussion

To compare the reducing ability of dihydropyridines with different substituents, the reactions between BNAH **1** and

1-arylpiperidinium salts **2** (Eq. 1), and between 1-(4-methylphenyl)-1,4-dihydropyridine **4b** and 1-aryl-3-carbamoylpyridinium (1-arylnicotinamide) **5** (Eq. 2) were carried out.



X = 4-OCH₃(a), 4-CH₃(b), H(c), 4-Cl(d), 4-CN(e), 2,4-dinitro(f)



X = 4-OCH₃(a), 4-CH₃(b), H(c), 4-Cl(d), 4-NO₂(e), 2,4-dinitro(f)

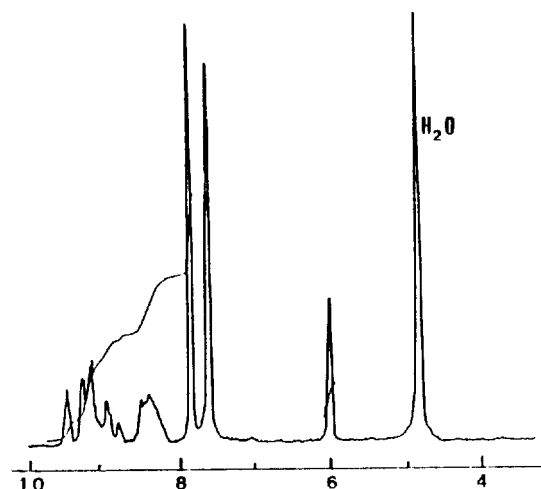


Figure 1. PMR spectrum of water-soluble portion of the reaction mixture of 1-benzyl-3-carbamoyl-1,4-dihydropyridine **1** and 1-phenylpyridinium chloride **2c**.

The compounds **1** and **4b** were chosen because of easiness in quantization of the reaction mixtures by nmr techniques discussed below.

After concentrating the reaction mixtures, water-insoluble components (dihydropyridines) were separated from the aqueous solution of pyridinium salts (water-soluble). The extents of reactions were determined from nmr integration data of the water-soluble and water-insoluble portions. A typical spectrum is shown in Figure 1 for water-soluble components of the reaction mixture between **1** and **2c**: this is the composite spectra of **2c** and **3** free of water-insoluble dihydropyridines, **1** and **4c**. Similarly, the nmr spectra of water-insoluble portion showed little evidence of contamination from the water-soluble pyridinium salts. This suggests that the dihydropyridines are quantitatively separated from pyridinium salts.

Peaks of nmr spectra can be easily assigned,^{10,11} and for calculation of the ratio of dihydropyridines or pyridinium salts in the reaction mixtures the integration data were used. For example of Figure 1, the peaks at δ 7.9 and δ 7.7 correspond to those of 5H of phenyl group in **2c** and 5H of phenyl group in **3**, respectively. Also, peak at δ 6.0 arises from 2H of methylene group in **3** and peaks at δ 8.1-9.7 are due to 4H of nicotinamide ring in **3** and 5H of pyridine ring of **2c**. Either of ratios of these shows that **2c** and **3** are present in the ratio of 49:51 in this mixture. To ensure the equilibrium, we ran the reactions for 6 hours in addition to normal 3 hours. Also, the reverse reactions of Eqs. 1 and 2 were carried out. In all case, we obtained virtually same results indicating that the compositions of the reaction mixtures are in equilibrium.

Since we carried out the reaction in 1:1 mole ratio and no appreciable side products were detected, the ratio of two dihydropyridines (ratio of **1** and **4**, for example of Eq. 1) from nmr data of water-insoluble portion would be same as that of two pyridinium salts (ratio of **2** and **3**) obtained from nmr spectrum of water-soluble portion. Indeed, the ratio agreed well within experimental error range (5%). We took average of both ratios and the results are summarized in Table 1.

We also calculate the equilibrium constants of the reactions of Eq. 1. The equilibrium constants *K* are related to the standard Gibbs free energy change of the corresponding reactions by Eq. 3.

Table 1. Extents of Reactions and Equilibrium Constants of reactions between 1-Benzyl-3-carbamoyl-1,4-dihydropyridine **1** and 1-Arylpiperidinium Salts **2** (Eq. 1), and Estimated Standard Gibbs Free Energy Changes for Reduction of 1-Arylpiperidinium Salts.

Compds.	X	Ext. of Rex.(%)	K	ΔG° , KJ/mole
2a	4-OCH ₃	4	0.0017	16.1
2b	4-CH ₃	15	0.031	8.8
2c	H	51	1.08	-0.19
2d	4-Cl	91	102	-11.7
2e	4-CN	100 ^b	1.3×10^{6c}	-35.6 ^c
2f	2,4-dinitro	100 ^b	—	—

^aThese values defined at 30°C in ethanol are calculated from $-RT \ln K$ and with respect to the value for BNA/BNAH couple. ^bThe reactions proceeded nearly quantitatively, and therefore we could not estimate *K* and ΔG° for these reactions directly. ^cThese values are estimated from the Hammett plot in Figure 2.

$$(G_{DHP} - G_{PS}) - (G_{BNAH} - G_{BNA}) = -RT \ln K \quad (3)$$

DHP, PS, BNAH and BNA stand for the compounds **4**, **2**, **1** and **3**, respectively. The standard free energy change for the reduction of **2** with respect to BNA/BNAH couple, ΔG° , is simply $-RT \ln K$ and the values were included in Table 1. This Table shows that the reduction of 1-arylpiperidinium salts **2** by BNAH **1** becomes more favorable when the substituent at 1-position of **2** is more electron-withdrawing, i.e., the reducing power of dihydropyridines becomes less as the 1-substituent is more electron-withdrawing.

To correlate the reducibility of 1-arylpiperidinium salts with the characteristics of the substituents in 1-aryl moiety, we plotted the $\log K$ and ΔG° against σ_p of the substituents. The results are shown in Figure 2. The Hammett plot shows good linear correlation ($r = 0.997$) with reaction constant ρ of 9.4 (for $\log K$) and -54.5 KJ/mole (for ΔG°). This result matches well with the observation of the correlation between rate constants of reduction of N-methylacridinium ion by 1-aryl-1,4-dihydropyridines and σ values of the substituents.¹³ This is an indication of high sensitivity of the reducibility of pyridinium salts, i.e., reducing power of

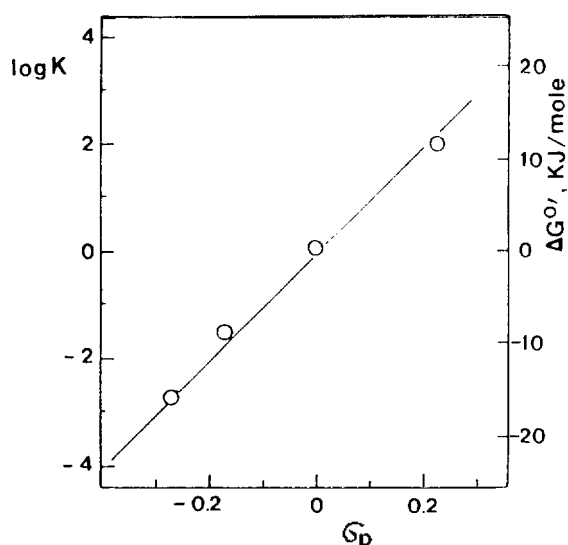


Figure 2. Hammett plot for logarithm of equilibrium constants and standard Gibbs free energy change of reactions in Eq. 1 ($r = 0.997$). The σ_p values were taken from Ref. 12.

dihydropyridines, on the electron-withdrawing nature of the 1-substituent and suggests the reducing power of dihydropyridines are greatly affected by the lone-pair electron density on the ring nitrogen.

The reduction of 1-arylnicotinamides **5** by 1-(4-methylphenyl)-1,4-dihydropyridine **4b** proceeded quantitatively to the forward direction, except for the reduction of 1-(4-methoxyphenyl) nicotinamide **5a** of which extent of reaction was 96%. The latter value gives equilibrium constant of 580 for the reaction between **4b** and **5a**, and standard Gibbs free energy change of -16 KJ/mole for the reduction of **5a** with respect to **2b/4b** couple. If one assumes that the same Hammett relationship is applied for both pyridinium **2** and 3-carbamoylpyridinium salts **5**, the equilibrium constant for the reaction of **4b** with **5b** would be 5000 and the difference in standard Gibbs free energy of reduction of **5b** with respect to the same of **2b** is estimated to be -21.5 KJ/mole.¹⁴ Similar K value is expected for reactions between pairs of dihydropyridine **4** and nicotinamide salt **5** bearing the same 1-substituent. Also, reduction of a compound by dihydropyridine **4** would be energetically more favorable than the corresponding reduction by dihydronicotinamide **6** having the same 1-substituent by as much as 21.5 KJ/mole, i.e., -223 mV in terms of standard redox potential.

So far we have shown that 1,4-dihydropyridine **4** is more powerful reducing agent than the corresponding 1,4-dihydronicotinamide **6**, and the reducing power becomes less when electron-withdrawing group is attached to the pyridine ring.¹⁵ In this aspect, it is surprising to note that it has been generally granted that the 3-carbamoyl moiety is necessary for 1,4-dihydropyridines to be effective as reducing agent. Only few 1,4-dihydropyridines without 3-carbamoyl group were tested.^{16,17} The group rather decreases the reducing ability of the dihydropyridines. However, it might play a critical role in the formation of NAD(P)H-enzyme complexes or in dihydronicotinamide-substrate interaction when dihydronicotinamide is utilized as a reducing agent.

The pyridinium salts with highly electron-withdrawing groups become very base-labile¹⁸, thus the compounds **4f**, **6e**

and **6f** could not be obtained by conventional dithionite reduction¹¹ of the corresponding pyridinium salts, which requires basic condition. For these cases, the reactions of Eqs. 1 and 2 provide convenient means for preparation of 1,4-dihydropyridines.

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References

1. NADH and NADPH are abbreviations of reduced form of nicotinamide adenine dinucleotide (NAD⁺) and nicotinamide adenine dinucleotide phosphate (NADP⁺), respectively.
2. U. Eiser and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).
3. D. M. Stout and A. I. Meyers, *Chem. Rev.*, **82**, 223 (1982).
4. Y. Inouye, J. Oda and N. Baba, in 'Asymmetric Synthesis', J. D. Morrison Ed., Academic Press, New York, Vol. 2 pp. 91-124, 1983.
5. D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 2261 (1955).
6. Some recent works are: (a) Y. Ohnishi, M. Kagami and A. Ohno, *J. Am. Chem. Soc.*, **97**, 4799 (1975); (b) D. J. Creighton, J. Hajdu and D. S. Sigman, *J. Am. Chem. Soc.*, **98**, 4619 (1976); (c) A. Ohno, H. Yamamoto and S. Oka, *J. Am. Chem. Soc.*, **103**, 2041 (1981); (d) A. Ohno, Y. Ishihara, S. Ushida and S. Oka, *Tetrahedron Lett.*, 3185 (1982); (e) N. Baba, M. Amano, J. Oda and Y. Inouye, *J. Am. Chem. Soc.*, **106**, 1481 (1984).
7. (a) S. Shinkai, H. Hamada, A. Dohyama and O. Manabe, *Tetrahedron Lett.*, 1661 (1980); (b) M. de Niesarink and U. Pandit, *Tetrahedron Lett.*, 2449 (1979).
8. (a) S. H. Mashraqui and R. M. Kellogg, *J. Am. Chem. Soc.*, **105**, 7792 (1983); (b) A. I. Meyers and T. Oppenlaender, *J. Am. Chem. Soc.*, **108**, 1989 (1986).
9. K. E. Taylor and J. B. Jones, *J. Am. Chem. Soc.*, **98**, 5689 (1976).
10. K. K. Park, J. Lee and D. Han, *Bull. Kor. Chem. Soc.*, **6**, 141 (1985).
11. K. K. Park, D. Han and D. Shin, *Bull. Kor. Chem. Soc.*, **7**, 201 (1986).
12. C. D. Johnson, "The Hammett Equation," Cambridge Univ. Press, p. 4, 1973.
13. A. Ohno, T. Shio, H. Yamamoto and S. Oka, *J. Am. Chem. Soc.*, **103**, 2045 (1981).
14. The σ_p values of 4-OCH₃ and 4-CH₃ are -0.27 and -0.17, respectively. This difference results in the difference of log K and $\Delta G^{\circ'}$ by 0.94 and -5.5 KJ/mole from the Hammett plot.
15. What we demonstrated is that the nicotinamide salt **5** is more easily reduced than the corresponding pyridinium salts **2**. Consideration of the reverse reaction leads to this conclusion.
16. D. C. Dittmer, A. Lombardo, F. H. Batzold and C. S. Greene, *J. Org. Chem.*, **41**, 2976 (1976).
17. M. M. Kreevoy and I.-S. H. Lee, *J. Am. Chem. Soc.*, **106**, 2550 (1984).
18. D. J. Norris and R. Steward, *Can. J. Chem.*, **55**, 1687 (1977).