

Reduction of *N*-Arylpyridinium Compounds by Sodium Borohydride and Dithionite: Regioselectivity and Isomerization of Reduction Products

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Reduction of *N*-arylpyridinium compounds by NaBH₄ gave mixtures of the corresponding 1,2-dihydropyridine(major) and 1,4-dihydropyridine(minor), whereas similar reduction by Na₂S₂O₄ produced 1,4-dihydropyridines regioselectively. The proportion of 1,4-isomer in the product by NaBH₄ reduction appeared to increase with the electron-donating ability of *N*-aryl groups. When the *N*-aryl group is *p*-methylphenyl, *p*-ethylphenyl or *p*-methoxyphenyl, the 1,2-dihydropyridines in ethanol-water (4:1) solutions isomerized to the corresponding 1,4-dihydropyridines. *N*-(*p*-methylphenyl)-1,2-dihydropyridine and *N*-(*p*-ethylphenyl)-1,2-dihydropyridine in solid state also isomerized to the corresponding 1,4-dihydropyridines. The different behaviors of reduction among *N*-arylpyridiniums and isomerization of the reduction products depending on the substituent in *N*-aryl group were explained in terms of difference in the electronic effects of the substituents.

Introduction

Reduction of pyridinium compounds has attracted much concern in relation to the importance of dihydropyridine chemistry.¹ The recent interest in dihydropyridines can be traced to the coenzyme, reduced nicotinamide adenine dinucleotide(NADH), and the unique ability of these compounds in biological systems to reduce unsaturated functionalities. Thus, considerable efforts have been made in synthesizing NADH mimics, exploring the reactions and mechanisms involving these compounds, and utilizing them in a variety of synthetic reactions.²

In contrast to the formation of 1,4-dihydro compounds from reduction of nicotinamide adenine dinucleotide(NAD⁺) in biological systems, chemical reduction of pyridinium salts gives different reduction products depending on the reducing agents and substrates.³⁻⁸ However, the mechanism of the reductions has not been fully understood. Therefore, it would be of interest to study the reduction of *N*-arylpyridinium salts, in which aryl groups with various substituents differing in electronic effect can be easily incorporated,⁹ and to compare their reduction products. It is also known that some of 1,2-dihydroquinolines isomerize to the corresponding 1,4-isomers.¹⁰ The study on the isomerization of *N*-aryldihydropyridines is expected to give valuable informations on the factors underlying the process.

In this paper, we report the reduction of *N*-arylpyridinium salts by sodium dithionite(Na₂S₂O₄) and sodium borohydride (NaBH₄). Structures and ratios of isomers of the reduction products, and the isomerization between them are presented.

Experimental

Pmr spectra were taken from a Varian FT-80A spectrometer using CDCl₃ as a solvent, and chemical shifts were expressed as units relative to TMS. Melting points, uncorrected, were determined on a Electrothermal Melting Point

Apparatus. *N*-Arylpyridinium chloride (XC₆H₄-N⁺) Cl⁻: X

=H, *p*-Me, *p*-Et, *p*-Cl, *p*-OMe) were prepared by reacting 2,4-dinitrophenylpyridinium chloride with the corresponding aniline derivatives according to the procedure described elsewhere.⁹ Unspecified chemicals were com-

mercially available reagent-grade, and distilled water was used.

General Procedure for Reduction of *N*-Arylpyridinium Chlorides by NaBH₄. 3 mmol of *N*-arylpyridinium chloride was dissolved in 85 ml of water containing 0.34 g(6 mmol) of KOH. To this solution, 0.11 g(3 mmol) of NaBH₄ (Nisso-Ventron; 98 % Min.) in 50 ml of water was added. The reaction mixture was stirred for 2 hrs at room temperature under nitrogen atmosphere and then filtered to obtain yellow solid product. Recrystallization of this product from methanol gave a mixture of the corresponding 1,2- and 1,4-dihydropyridine derivatives.

General Procedure for Reduction of *N*-Arylpyridinium Chlorides by Na₂S₂O₄. 3 mmol of *N*-arylpyridinium chloride was dissolved in 50 ml of water, and 1.38 g of Na₂CO₃ and

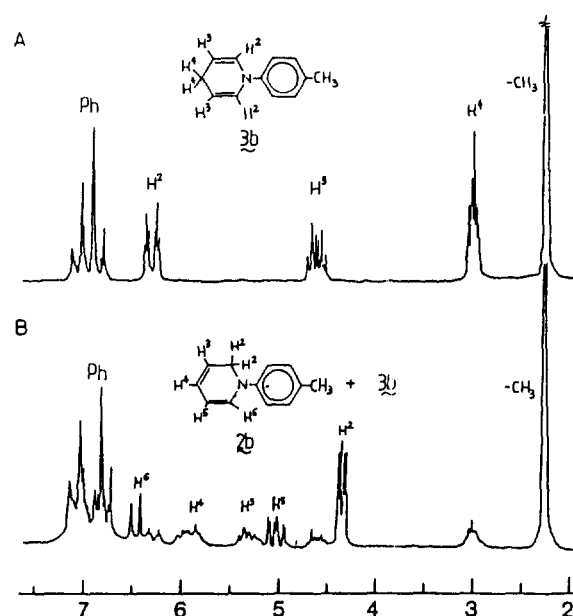


Figure 1. Proton NMR spectra of *N*-(*p*-methylphenyl)-1,4-dihydropyridine, **3b** obtained from Na₂S₂O₄ reduction(A) and a mixture of *N*-(*p*-methylphenyl)-1,2-dihydropyridine, **2b**(major) and *N*-(*p*-methylphenyl)-1,4-dihydropyridine, **3b**(minor) obtained from NaBH₄ reduction(B). Peak assignments are shown. The remaining peaks in B are from the 1,4-isomer, **3b**.

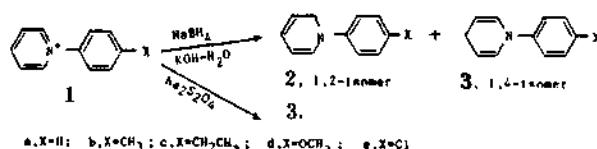
1.85 g of $\text{Na}_2\text{S}_2\text{O}_4$ (Hayashi Pure Chemicals) were added to the solution. Warming the solution at 35–50°C for 0.5 hr yielded yellow flocculent solid. Filtration and recrystallization of the product from methanol gave the corresponding 1,4-dihydropyridine derivative.

Isomerization Between 1,2- and 1,4-Dihydropyridine Derivatives in Solid State. The product obtained from the reduction of N-arylpyridinium compound by NaBH_4 was air dried and its nmr spectrum was taken. After standing the solid at room temperature in dark for desired period, its nmr spectra were retaken. The ratios of 1,2- and 1,4-dihydropyridines were determined from the integral data of the nmr spectra.

Isomerization Between 1,2- and 1,4-Dihydropyridine Derivatives in Solution. 1.5–2.0 g of reaction product from NaBH_4 reduction was dissolved in 250 ml of ethanol-water(4:1). After storing the solution at room temperature under nitrogen atmosphere for appropriate period, part of the solution was taken and the solvent was evaporated under reduced pressure to obtain a solid mixture. The ratio of isomers of this mixture was calculated from the intergral data of nmr spectrum of the mixture.

Results and Discussion

Reduction of N-arylpyridinium ions **1** by NaBH_4 gave a mixture of the corresponding N-aryl-1,2-dihydropyridine **2** and N-aryl-1,4-dihydropyridine **3**, whereas the reduction by sodium dithionite yielded exclusively the corresponding 1,4-isomers.



The definite structural assignments of the reaction products could be made from their nmr spectra.³ Typical nmr spectra of the products are shown in Figure 1: the spectrum in Figure 1A can be assigned to that of 1,4-dihydropyridine, since it shows only two kinds of olefinic hydrogens, while the spectrum in Figure 1B can be attributed to that of 1,2-dihydropyridine containing a small amount of 1,4-isomer. Subtracting the peaks corresponding to 1,4-isomer (Figure 1A) from Figure 1B leaves the spectrum of the 1,2-isomer, which exhibits four kinds of olefinic hydrogens. The nmr spectral data of N-aryl-1,2-dihydropyridines and N-aryl-1,4-dihydropyridines are summarized in Table 1 and 2, respectively.

As 1,2-isomer has quite different chemical shifts from that of the corresponding 1,4-isomer, the ratio of these isomers in the products of NaBH_4 reduction can be easily estimated from the integral data of the nmr spectrum of the products. The results are given in Table 3.

It was reported that reduction of N-phenylpyridinium salt with NaBH_4 gives a mixture of 1,2- and 1,4-dihydropyridine,³ whereas the same reduction of N-alkylpyridinium salts produces tetrahydropyridines and piperidines;⁵ the difference was explained in terms of the electron-withdrawing character of phenyl group.¹¹ The mechanism for borohydride

Table 1. Nmr data of N-Aryl-1,2-dihydropyridines

Subst.	X	Chemical shift(δ)						Phenyl	X
		H ²	H ¹	H ⁴	H ³	H ⁶			
2a	H	4.34 (d of d)	5.5–5.2 (m)	6.1–5.75 (m)	5.2–4.9 (m)	6.48 (d)	7.4–6.8 (m, 5H)		
2b	CH ₃	4.34 (d of d)	5.4–5.1 (m)	6.1–5.75 (m)	5.1–4.8 (m)	6.45 (d)	7.2–6.7 (m, 4H)	2.26 (s, 3H)	
2c	C ₂ H ₅	4.34 (d of d)	5.4–5.1 (m)	6.1–5.75 (m)	5.1–4.8 (m)	6.45 (d)	7.2–6.7 (m, 4H)	1.20(t, 3H) 2.57(q, 2H)	
2d	OCH ₃	4.33 (d of d)	5.4–5.1 (m)	6.1–5.75 (m)	5.1–4.8 (m)	6.40 (d)	6.83 (s, 4H)	3.76 (s, 3H)	
2e	Cl	4.29 (d of d)	5.5–5.2 (m)	6.1–5.75 (m)	5.2–4.9 (m)	6.40 (d)	7.3–6.6 (m, 4H)		

Coupling constants were $J_{13}=4$, $J_{14}=2$ and $J_{36}=8$ Hz.

Table 2. Yields, Melting Points and Nmr Data of N-Aryl-1,4-dihydropyridines Obtained by Dithionite Reduction of N-Arylpyridinium Chlorides

Subst.	X	yield (%)	mp (°C)	Chemical shift(δ)				
				H ²	H ¹	H ⁴	phenyl	X
3a	H	61	48	6.35 (t of d)	4.63 (t of d)	3.1–2.9 (m)	7.4–6.8 (m, 5H)	
3b	CH ₃	58	57	6.28 (t of d)	4.59 (t of d)	3.1–2.9 (m)	7.2–6.7 (m, 4H)	2.26 (s, 3H)
3c	C ₂ H ₅	41	54	6.28 (t of d)	4.59 (t of d)	3.1–2.9 (m)	7.2–6.7 (m, 4H)	1.20(t, 3H) 2.57(q, 2H)
3d	OCH ₃	63	81	6.20 (t of d)	4.55 (t of d)	3.1–2.9 (m)	7.0–6.7 (m, 4H)	3.76 (s, 3H)
3e	Cl	60	80	6.27 (t of d)	4.66 (t of d)	3.1–2.9 (m)	7.3–6.7 (m, 4H)	

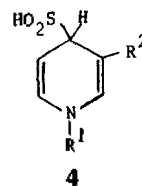
Coupling constants were $J_{23}=8.5$, $J_{24}=2$ and $J_{34}=4$ Hz.

reduction of pyridinium salts was suggested as involvement of initial irreversible nucleophilic attack by hydride ion at the 2 and/or 4 positions of pyridine nucleus to generate the corresponding dihydropyridines.¹¹ It was also suggested that addition of a hydride ion at the 2 position is kinetically favored because the site is closest to the positive nitrogen and therefore, most favored by coulombic attraction. Our results in Table 3 support these explanations: the amount of 1,4-isomer in the reduction products increases with the electron-donating ability, *i.e.*, the effectiveness for neutralization of the positive charge on nitrogen, of substituents at the para position of phenyl ring. Of course, the preference for the position of the hydride addition would also be affected by steric factors, and a bulky substituent on the nitrogen would sterically interfere with the approach of the hydride ion to the 2-position.⁵ However, this factor may not be significantly different among *N*-arylpyridinium ions used in this study.

Sodium dithionite has been used for reduction of many organic compounds.¹² It is generally known that pyridinium salts are reduced by dithionite only when electron-withdrawing groups are attached to 3 or 5 position of the pyridinium nucleus, and the reduction produces almost exclusively the corresponding 1,4-dihydropyridine.^{10,10,11,14} In agreement with these reports, our attempts of dithionite reduction of simple *N*-alkylpyridinium salts (alkyl = methyl, propyl or benzyl) were failed. However, the same reduction of *N*-arylpyridinium salts gave 1,4-dihydropyridines, exclusively. In our knowledge, this is the first example of 1,4-dihydropyridine formation by dithionite reduction of pyridinium salts, which do not bear electron-withdrawing group in the 3 or 5 position.

The difference in the regionality of reduction between NaBH_4 and $\text{Na}_2\text{S}_2\text{O}_4$ reductions points that the reduction mechanisms are different. Unlike reduction by NaBH_4 , the

reduction by $\text{Na}_2\text{S}_2\text{O}_4$ appeared to involve sulfinate adduct **4**, as an intermediate.^{13,14}



If the sulfinate adduct transforms to the corresponding dihydropyridine intramolecularly, the regioselectivity of the reduction would be determined by that of the C-S bond formation, which appeared to show the thermodynamic preference for the 4-position.¹³ The proposed mechanism for the reduction of NAD^+ analogues by $\text{Na}_2\text{S}_2\text{O}_4$, which attributed HSO_2^- to the hydride donor,¹¹ can not explain the regioselectivity. Similarity between *N*-arylpyridinium salts and pyridinium salts bearing electron-withdrawing group at 3 or 5-position of pyridine nucleus in reduction of these salts by $\text{Na}_2\text{S}_2\text{O}_4$ implies that the partial positive charge at the 4-position of the pyridinium nucleus might play a critical role in the reduction. This partial charge can be induced by resonance or inductive effect from the substituents at nitrogen, 3 or 5 position.

Table 4 shows the changes of the amounts of *N*-aryl-1,4-dihydropyridines on standing the initial mixtures of 1,2- and 1,4-isomers obtained by NaBH_4 reduction, in ethanol-water (4:1) solution and in solid state. Compounds **2b**, **2c** and **2d** isomerized slowly to the corresponding 1,4-isomers, **3b**, **3c**, and **3d**, in the solution. However, *N*-phenyl-1,2-dihydropyridine (**2a**) and *N*-(*p*-chlorophenyl)-1,2-dihydropyridine (**2e**) did not behave similarly. It was also observed that **2b** and **2c** transform spontaneously to **3b** and **3c**, respectively, in solid state. But no noticeable evidence of such transformation was detected for **2a**, **2d**, and **2e** on standing these compounds in solid state even for more than a week. Similar isomerization of 1,2-dihydroquinolines to the corresponding 1,4-dihydroquinolines was also reported, and the isomerization appeared to be thermodynamically controlled.

The stability of **2a** and **2e** to isomerization in solution as well as in solid state indicates that the initial isomer compositions of reduction products shown in Table 3 are results of direct attack of hydride ion at 2- and 4-positions of the pyridinium ions. Since reduction by NaBH_4 was carried out at room temperature for ca. 2 hours, it is hardly expected that the isomerization takes place to a considerable extent to make a meaningful effect on the isomer ratios of the initial reduction products. Thus, the same conclusion can be drawn for the other isomer compositions listed in Table 3.

It is of interest to note that **2a** and **2e**, which do not isomerize under these experimental conditions, are formed in largest isomeric ratio during the reduction of **1a** and **1e** by NaBH_4 . This can be taken as an implication that the same factor, presumably the electronic effect of *N*-substituent, contributed to the formation of the 1,4-isomer by reduction (kinetically) and by isomerization (thermodynamically). However, we can not rule out the possibility that the correlation is fortuitous. If this is the case, the stability of **2a** and **2e** against isomerization seems to reflect the kinetic stability of them.

Table 3. Yields and Isomer Compositions of the Reduction Products of *N*-Arylpyridinium Chlorides by NaBH_4 .

Subst. X	Yield(%)	Composition(%)	
		1,2-isomer	1,4-isomer
Cl	62	91	9
H	64	89	11
CH_3	61	86	14
C_2H_5	58	82	18
OCH_3	71	76	24

Yields are combined values for 1,2- and 1,4-isomers.

Table 4. Changes of the Amounts of *N*-Aryl-1,4-dihydropyridines on Standing in Solution and in Solid State*

	Subst. X	Initial	1,4-isomer(%)	
			solution	solid
a	H	11	N.C.***	N.C.
b	CH_3	14	26	27
c	C_2H_5	18	28	36**
d	OCH_3	24	34	N.C.
e	Cl	9	N.C.	N.C.

* Standing times are 36(solution) and 82(solid) hours. ** This value was taken after 48 hours due to decomposition. *** N.C. is less than 2% change, which is about the error range.

The solid state isomerization of **2b** and **2c** is quite unusual and joins rare examples of solids that undergo chemical transformation in solid state, spontaneously. Interestingly, **2d** does not isomerize in solid state, though it does in solution. This indicates clearly that the solid state isomerization depends on the crystalline structure of the solid.

Acknowledgement. This work was supported by the Basic Science Research Institute Program of the Ministry of Education of the Republic of Korea, 1985.

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On Stability of the Steady State, Thermodynamic Stability and Corresponding States in Rheology of Dense Simple Fluids[†]

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Received February 24, 1986

It is shown that the linear stability coincides with the thermodynamic stability in the case of stress tensor evolution for simple dense fluids even if the constitutive (evolution) equation for the stress tensor is nonlinear. The domain of coincidence can be defined in the space of parameters appearing in the constitutive equation and we find the domain is confined in an elliptical cone in a three-dimensional parameter space. The corresponding state theory in rheology of simple dense fluids is also further examined. The validity of the idea is strengthened by the examination.

Introduction

Viscous phenomena¹ have attracted attention from physical scientists and engineers over a few decades by now since the subject is relevant to various engineering questions as well as some fundamental physical aspects of matter. Especially,

non-Newtonian viscous flow of polymeric materials presents an interesting object of study since they are not only important substances in our everyday life but also present often intriguing and challenging topics of investigation in chemistry and physics. In the past a great deal of effort has been invested into the investigations² of empirical rheological equations of state and their statistical foundations which are generally studied by means of the Brownian motion model of a polymer taken as a bead-spring.³

[†] Supported in part by the Natural Sciences and Engineering Research Council of Canada.