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Fine Control of Regioselectivity in the Reduction of NAD^+ Analogues by Ketene Silyl Acetals

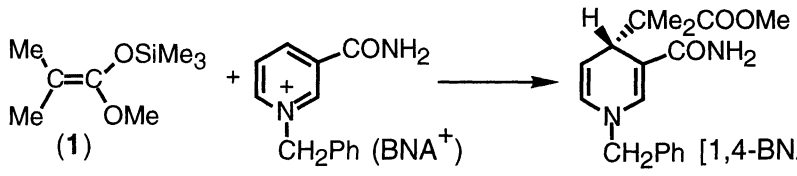
Shunichi FUKUZUMI,* Morifumi FUJITA, Souta NOURA, and Junzo OTERA*†
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565
†Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700

Various NAD^+ analogues are reduced regioselectively by ketene silyl acetals to afford the corresponding 2-, 6-, or 4-alkylated NADH analogues. The regioselectivity of the 1,2- (or 1,6-) *vs.* 1,4- reduction is finely controlled by the β-methyl-substitution of ketene silyl acetals, the position of methyl-substitution of NAD^+ analogues, and the addition of Et_4NCl or Bu_4NF.

Reduction of pyridinium and quinolinium ions by organometallic reagents to yield the reduced alkyl adducts has accepted increasing interest in relation with the important role as the valuable synthetic intermediates for a variety of alkaloids as well as analogues of dihydronicotinamide adenine dinucleotide (NADH).[1-4] With respect to oxidants, however, they have so far been limited to pyridines and quinolines activated by alkyl chloroformate. The control of the regioselectivity of these reactions has been of critical importance in synthetic and mechanistic point of view.[1-4]

We have recently reported that 10-methylacridinium perchlorate ($AcrH^+ClO_4^-$) is readily reduced by ketene silyl acetals to yield the alkylated products.[5] We report herein that various NAD^+ analogues in which the regioselectivity of the reduction becomes an issue are reduced regioselectively by ketene silyl acetals to yield the alkylated NADH analogues and that the regioselectivity is finely controlled by the β-methyl-substitution of ketene silyl acetals, the position of methyl-substitution of NAD^+ analogues, and also by the addition of fluoride ion. The mechanistic insight into the regioreversed reduction of NAD^+ analogues by ketene silyl acetals is discussed based on the kinetic study.

It is found that the β,β-dimethyl-substituted ketene silyl acetal (**1**) can reduce various NAD^+ analogues, perchlorate salts of 1-benzylnicotinamidiun ion (BNA^+) and 1-methylquinolinium ions ($X\text{-}QuH^+$; X = 3-CN, 3-Br, H, and 2-Me) regioselectively at the 4-position to yield the corresponding 4-alkylated NADH analogues as shown in Eqs. 1 and 2, respectively. The yields of the alkylated products are shown in Table 1. The product



(1)

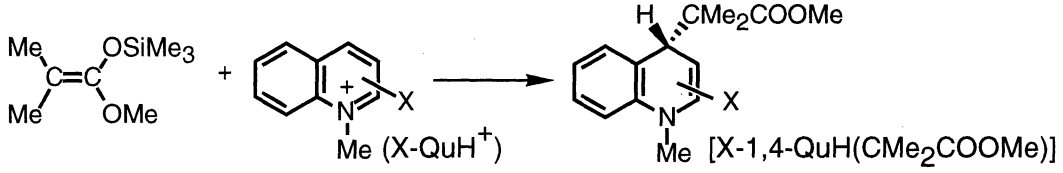


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Table 1. Regioselective Reduction of NAD^+ Analogues by Ketene Silyl Acetals in Acetonitrile at 298 K

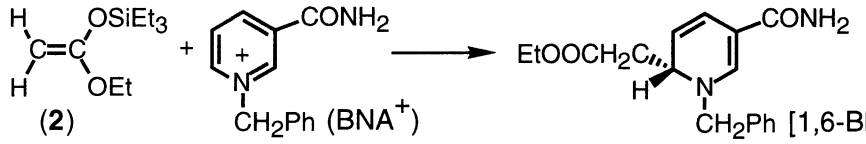
Ketene silyl acetal (M)[a]	NAD^+ analogue (M)	Additive (M)	Product (yield / %)[b]
1 (0.38)	BNA^+ (0.10)	Et_4NCl (0.10)	1,4-BNA(CMe_2COOMe) (100)
1 (0.38)	3-$CNQuH^+$ (0.10)	none	3-CN-1,4-Qu$H(CMe_2COOMe)$ (100)
1 (0.38)	3-$BrQuH^+$ (0.10)	none	3-Br-1,4-Qu$H(CMe_2COOMe)$ (100)
1 (0.28)	QuH^+ (0.10)	Et_4NCl (0.10)	1,4-Qu$H(CMe_2COOMe)$ (100)
1 (0.38)	2-$MeQuH^+$ (0.10)	Et_4NCl (0.10)	2-Me-1,4-Qu$H(CMe_2COOMe)$ (100)
1 (0.38)	4-$MeQuH^+$ (0.10)	Et_4NCl (0.10)	4-Me-1,2-Qu$H(CMe_2COOMe)$ (100)
2 (0.10)	BNA^+ (0.010)	Et_4NCl (0.04)	1,6-BNA(CH_2COOEt) (100)
2 (0.10)	2-$MeQuH^+$ (0.010)	Et_4NCl (0.10)	no reaction
2 (0.10)	4-$MeQuH^+$ (0.010)	Et_4NCl (0.10)	4-Me-1,2-Qu$H(CH_2COOEt)$ (100)
2 (0.10)	QuH^+ (0.010)	Et_4NCl (0.10)	1,2-Qu$H(CH_2COOEt)$ (100)
1 (0.38)	QuH^+ (0.10)	Bu_4NF (0.10)	1,2-Qu$H(CMe_2COOMe)$ (67) 1,4-QuH(CMe2COOMe) (33)
1 (0.10)	4-$MeQuH^+$ (0.010)	Bu_4NF (0.10)	4-Me-1,2-Qu$H(CMe_2COOMe)$ (100)
1 (0.38)	2-$MeQuH^+$ (0.10)	Bu_4NF (0.10)	2-Me-1,4-Qu$H(CMe_2COOMe)$ (100)

a) 1 M = 1 mol dm^{-3}. b) The product yields were determined by ^1H NMR (400 MHz).

yields were determined by ^1H NMR (JEOL JNM-GSX-400) as reported previously.[6] No isomerization of the 4-alkylated products has been observed during the reactions. Such selective 1,4-reduction of X-QuH^+ by **1** shows a sharp contrast with the selective 1,2-reduction of X-QuH^+ by a *trans*-dimethylcobalt(III) complex to yield the 2-methyl-1,2-dihydroquinoline derivatives (X-1,2-QuHMe).[6]

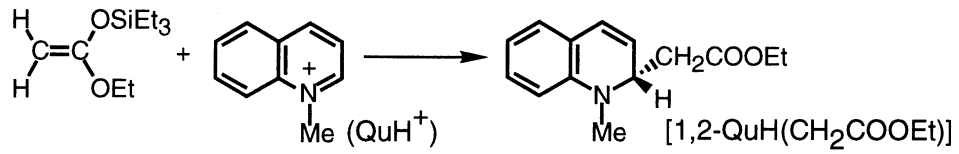
The addition of Et_4NCl is required to complete the reactions except for the reduction of 3-$CNQuH^+$, and 3-$BrQuH^+$ (Table 1). When a large excess of ketene silyl acetals is employed, however, the reaction undergoes to completion in each case. Thus, the reactions of ketene silyl acetals with X-QuH^+ and BNA^+ (Eqs. 1 and 2) may be reversible, and the trap of silyl perchlorate formed initially by Et_4NCl may compete well with the backward reaction of silyl perchlorate with the alkylated NADH analogues. When the 4-position is blocked by methyl group in the case of 4-$MeQuH^+$, the reduction by **1** occurs at the 2-position exclusively to yield the 2-alkylated product (Table 1).

The ketene silyl acetal (**2**) being less hindered than **1** also reduce X-QuH^+ and BNA^+ regioselectively, but the regioselectivity is completely reversed as compared with the case of **1**; the reduction of BNA^+ and X-QuH^+ [X = H and 4-Me] occurs at the 6- and 2-position to yield the 6- and 2-alkylated products as shown in Eqs. 3



(3)

and 4, respectively (Table 1).[7] When the 2-position is blocked by the methyl group in the case of 2-$MeQuH^+$, no reduction by **2** takes place (Table 1).



(4)

The reaction rates were determined by the change in the electronic spectra.[8] The observed second-order rate constants (k_{obsd}) are summarized in Table 2, together with the one-electron reduction potentials of NAD^+ analogues.[9] The k_{obsd} value of the reduction of NAD^+ analogues by **1** decreases with a decrease in the E^0_{red} value (Table 2), when the LUMO becomes deeper. Therefore, the reactivity of NAD^+ analogues seems essentially frontier controlled. In such a case, the regioselectivity may be controlled by the magnitude of atomic coefficients in the LUMO of NAD^+ analogues, which is known to be the largest at the 4-position.[6] Since the HOMO of β,β-dimethyl-substituted ketene silyl acetal (**1**) is mainly localized at the β-position, [10] the HOMO-LUMO interaction may lead to the C-C bond formation between the β-position of **1** and the 4-position of NAD^+ analogues to yield the 4-alkylated products (Eqs. 1 and 2). On the other hand, electron transfer from **1** to NAD^+ analogues is expected to give the same regioselectivity and the rate would decrease with a decrease in the E^0_{red} value as shown in Table 2. However, the outer-sphere electron transfer pathway in the present case is unlikely judging from the positive one-electron oxidation potential of **1** (E^0_{ox} *vs.* SCE = 0.90 V)[10] and the largely negative E^0_{red} values of NAD^+ analogues (Table 2), when the electron transfer is highly endergonic.

Table 2. Rate Constants (k_{obsd}) of the Reduction of NAD^+ Analogues by Ketene Silyl Acetals in MeCN at 298 K and the One-Electron Reduction Potentials (E^0_{red}) of NAD^+ Analogues

NAD^+ analogue	E^0_{red}[a] vs. SCE / V	Ketene silyl acetal	k_{obsd} M^{-1} s^{-1}
$AcrH^+$	-0.43	**1**	6.7×10^1
3-$CNQuH^+$	-0.60	**1**	2.3×10^1
3-$BrQuH^+$	-0.76	**1**	1.6×10^{-1}
QuH^+	-0.96	**1**	3.1×10^{-2}
QuH^+	-0.96	**1**[b]	3.1×10^1
2-MeQuH^+	-1.05	**1**	1.6×10^{-2}
4-MeQuH^+	-1.07	**1**	1.4×10^{-2}
BNA^+	-1.08	**1**	7.4×10^{-3}
QuH^+	-0.96	**2**	5.9×10^{-2}
2-MeQuH^+	-1.05	**2**	no reaction
4-MeQuH^+	-1.07	**2**	1.0×10^{-2}
BNA^+	-1.08	**2**	2.8×10^{-2}

a) Ref. 5. b) In the presence of 0.030 M Bu_4NF.

The k_{obsd} value of the reduction of NAD^+ analogues by the less hindered ketene silyl acetal (**2**) than **1** is rather insensitive to the E^0_{red} value as compared with the case of **1** (Table 2), suggesting the stronger control by the charge rather than the HOMO-LUMO interaction. In contrast with the case of **1**, the HOMO of **2** is reported to be delocalized in the π-orbitals of the two sp2 carbons,[10] when the HOMO-LUMO interaction in the case of **2** is expected to be smaller than the case of **1**. Since the positive charge densities at 2 or 6-position of NAD^+ analogues are larger than those at 4-position,[6] the charge interaction between **2** and NAD^+ analogues may lead to afford the 6- or 2-alkylated products (Eqs. 3 and 4).[11] The rate of such a S_N2 process may be rather insensitive to the change in the E^0_{red} value, but sensitive to the steric effect . Thus, the introduction of methyl group at the 2-position of QuH^+ results in no reaction with **2** as shown in Table 2.

The addition of Bu_4NF instead of Et_4NCl results in the reverse of the regioselectivity in the reduction of QuH^+ by **1** from the selective 1,4-reduction in the presence of Et_4NCl to the predominant 1,2-reduction (67%) together with the 1,4-reduction (33%) as shown in Table 1. The fluoride ion is known to react with ketene silyl acetals to produce the nucleophilic enolate anions.[12] Thus, the reversed regioselectivity in the presence of Et_4NF indicates the change in the process from frontier control to the charge control.[13] The significant increase in the nucleophilic reactivity of the enolate anion of **1** is observed as compared to that of the parent molecule as shown in Table 2.

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