Regioselective Addition of 2-Nitropropane Anion to NAD$^+$ Analogues

Shunichi Fukuzumi,*[a] Morifumi Fujita,[a] Junichi Maruta[a] and Michel Chanon*[b]
[a] *Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan*
[b] *URA 1411, CNRS, Boite 561, Faculté des Sciences de Saint-Jérôme, 13397 Marseille, Cedex 13, France*

Various NAD$^+$ analogues have been reduced regioselectively by the tetramethylammonium salt of 2-nitropropane anion in acetonitrile at 298 K to yield the corresponding 4-alkylated NADH analogues. The one-electron oxidation potential of the tetramethylammonium salt of 2-nitropropane anion has been determined as 0.10 V (*vs.* SCE) by using second harmonic ac voltammetry as well as by analysing the cyclic voltammograms at various sweep rates. The rate constants for the reduction of NAD$^+$ analogues by 2-nitropropane anion ($>1 \times 10^6$ dm^3 mol^{-1} s^{-1}) are much larger than those estimated for outer-sphere electron transfer from 2-nitropropane anion to NAD$^+$ analogues based on the one-electron oxidation potential of 2-nitropropane anion and the one-electron reduction potentials of NAD$^+$ analogues. The origin of the regioselectivity is discussed in terms of the HSAB (hard and soft acids and bases) principle.

There has been considerable interest in the regioselective addition of nucleophiles to pyridinium ions owing to the synthetic utility of obtaining valuable intermediates for nitrogen heterocycles, and to the biological importance of the enzymatic regioselective reduction of nicotinamide adenine dinucleotide (NAD$^+$) by a variety of substrates to yield exclusively the corresponding 1,4-dihydronicotinamide (NADH).[1] The regioselectivity, namely the formation of 1,2-, 1,4-, or 1,6-isomers, has been demonstrated to be influenced significantly both by the reaction conditions and by the nature of the nucleophiles.[2-4] The mechanistic differences leading to the different isomers remain ambiguous, however.

On the other hand, the ability of strongly basic nucleophiles, such as 2-nitropropane anion, to bring about electron transfer radical chain nucleophilic substitutions ($S_{RN}1$) is well documented.[5-8] The chain reactions are known to be initiated by photoinduced electron transfer from nucleophiles to electrophiles,[6,7] or by electrochemical one-electron reduction of electrophiles.[8] Non-chain electron transfer pathways have also been reported in thermal nucleophilic substitution reactions of strongly basic carbanions.[9,10] However, it is difficult to distinguish between the electron transfer and alternative polar mechanisms without knowing the one-electron redox potentials of nucleophiles and electrophiles. The instability of the radical species produced by electron transfer oxidation and reduction of nucleophiles and electrophiles has precluded the reliable determination of the standard one-electron oxidation and reduction potentials of nucleophiles and electrophiles, respectively.

This study reports that regioselective addition of the tetramethylammonium salt of 2-nitropropane anion to various NAD$^+$ analogues occurs efficiently in acetonitrile at 298 K to yield exclusively the corresponding 4-alkylated NADH analogues. We have previously determined the one-electron reduction potentials of various NAD$^+$ analogues by analysing the cyclic voltammograms at various sweep rates.[10-12] This study also reports the one-electron oxidation potential of the tetramethylammonium salt of 2-nitropropane determined directly by using second harmonic ac voltammetry (SHACV)[13] as well as by analysing the cyclic voltammograms at various sweep rates. Thus, these data provide a valuable energetic basis for distinguishing electron transfer and polar mechanisms of the regioselective addition of nitropropane anion to NAD$^+$ analogues.

Experimental

Materials.—The lithium salt of 2-nitropropane was prepared as described in the literature.[14] The tetramethylammonium salt of 2-nitropropane anion was prepared by deprotonation of 2-nitropropane by tetramethylammonium hydroxide pentahydrate in deaerated MeCN. 10-Methylacridinium iodide was prepared by the reaction of acridine with methyl iodide in acetone, and was converted into the perchlorate salt (AcrH$^+$ ClO_4^-) by addition of magnesium perchlorate to the iodide salt, and purified by recrystallization from methanol.[10] Likewise, 1-methyl-X-quinolinium perchlorate (X-QuH$^+$$ClO_4^-$: X = H, 2-Me, 3-Br and 3-CN) and 1-methyl-3,5-dichloropyridinium perchlorate (3,5-Cl_2PyH$^+$$ClO_4^-$) were prepared by the reactions of the corresponding quinoline and pyridine derivatives with methyl iodide, followed by metathesis with magnesium perchlorate.[10] 1-Benzylnicotinamidinium perchlorate (BNA$^+$$ClO_4^-$) was prepared by reactions of nicotinamide with benzyl chloride, followed by the metathesis with magnesium perchlorate.[10] Acetonitrile, which was obtained commercially, was purified and dried with calcium hydride by the standard procedure and stored under nitrogen.[15]

Reaction Procedure.—Typically, to a deaerated [$^2H_3$]acetonitrile (CD_3CN) solution (0.8 cm^3) containing QuH$^+$$ClO_4^-$ (0.10 mol dm^{-3}) in an NMR tube was added the tetramethylammonium salt of 2-nitropropane (0.12 mol dm^{-3}). The products were analysed by ^{1}H NMR spectroscopy. The ^{1}H NMR measurements were recorded using a JEOL JNM-PS-100 or JNM-GSX-400 NMR spectrometer. AcrH(CMe_2NO_2): δ 1.38 (s, 6 H), 3.57 (s, 3 H), 4.80 (s, 1 H) and 6.93–7.53 (m, 8 H). 1,4-QuH(CMe_2NO_2): δ 1.34 (s, 3 H), 1.44 (s, 3 H), 3.29 (s, 3 H), 4.30 (d, 1 H, J 6.0 Hz) and 6.3–7.4 (m, 6 H). 3-CN-1,4-QuH(CMe_2NO_2): δ 1.31 (s, 3 H), 1.54 (s, 3 H), 3.40 (s, 3 H), 4.47 (s, 1 H) and 7.0–7.5 (m, 5 H). 3-Br-1,4-QuH(CMe_2NO_2): δ 1.29 (s, 3 H), 1.59 (s, 3 H), 3.30 (s, 3 H), 4.59 (s, 1 H) and 6.8–7.5 (m, 5 H). 2-Me-1,4-QuH(CMe_2NO_2): δ 1.31 (s, 3 H), 1.42 (s, 3 H), 2.05 (s, 3 H), 3.30 (s, 3 H), 4.17 (d, 1 H, J 6.0 Hz) and 6.9–7.4 (m, 5 H). 1,4-BNA(CMe_2NO_2): δ 1.33 (s, 3 H), 1.35 (s, 3 H), 4.27 (d, 1 H, J 5.5 Hz), 4.52 (s, 2 H), 4.66 (d, 1 H, J 5.5 Hz), 5.8 (br, 2 H), 6.30 (d, 1 H, J 7.5 Hz), 7.26 (s, 1 H) and 7.3–7.6 (m, 6 H). 3,5-Cl_2-1,4-PyH(CMe_2NO_2): δ 1.56 (s, 6 H), 3.12 (s, 3 H), 4.32 (s, 3 H) and 6.37 (s, 2 H).

The 1,4-isomers are readily distinguished from the 1,2- and 1,6-isomers by comparison of the observed ^{1}H NMR spectra with those of 1,4-, 1,2- and 1,6-isomers of methyl adducts reported previously.[11]

Spectral Measurements.—Typically, after an acetonitrile (MeCN) solution (0.4 cm^3) containing BNA$^+$$ClO_4^-$ (2.1×10^{-3} mol dm^{-3}) in a 1 mm quartz cuvette had been deaerated by

bubbling with argon gas, 5 μl portions of a deaerated acetonitrile solution of 2-nitropropane anion, prepared by deprotonation of 2-nitropropane (2.6×10^{-1} mol dm^{-3}) with tetramethylammonium hydroxide pentahydrate (3.3×10^{-2} mol dm^{-3}) in deaerated MeCN, were added to the cuvette by means of a microsyringe. Upon addition of 2-nitropropane anion, the reduction of BNA^+ was complete. The electronic spectra were measured by using a Shimadzu UV-160A spectrophotometer. Rates of the reactions of 2-nitropropane anion with NAD^+ analogues were monitored by measuring the rise of the absorbance due to the adducts or the decrease of the absorbance due to NAD^+ analogues using a Union SM-401 stopped-flow spectrophotometer. The reactions were complete within the dead time of the mixing, although the concentrations of the reactants decreased to 8×10^{-5} mol dm^{-3}, which is close to the detection limit. The minimum values of the rate constants were estimated to be 1×10^6 dm^3 mol^{-1} s^{-1}.

Theoretical Calculations.—The theoretical studies were performed using the PM3 molecular orbital method.[16] The MOPAC program (*QCPE*, Program No. 455), revised as OS/2 Version 5.01 for adaptation to use on a NEC PC computer was obtained through the *Japan Chemistry Program Exchange* (*JCPE*).[17] The calculations were also performed by using a COMTEC 4D RPC computer with the MOL-GRAPH program Ver. 2.8 from Daikin Industries Ltd. Final geometry and energetics were obtained by optimizing the total molecular energy with respect to all structural variables. The structural output was recorded by using the MOPC program (*JCPE* Program No. P038).

Electrochemical Measurements.—The cyclic voltammetry measurements were performed on a Hokuto Denko Model HA-301 potentiostat–galvanostat in deaerated MeCN containing 5×10^{-2} mol dm^{-3} $NBu^n_4ClO_4$ as the supporting electrolyte at 298 K. The measured potentials were recorded with respect to the saturated calomel electrode (SCE). The platinum microelectrode was routinely cleaned by soaking it in concentrated nitric acid, followed by repeating rinsing with water and acetone and drying at 353 K prior to use in order to avoid possible fouling of the electrode surface.

The second harmonic ac voltammetry (SHACV) measurements of the tetramethylammonium salt and lithium salt of 2-nitropropane anion were carried out with a BAS 100B electrochemical analyser in deaerated MeCN and dimethyl sulfoxide (DMSO) containing 0.10 mol dm^{-3} NBu^n_4 ClO_4 as the supporting electrolyte at 298 K, respectively. The platinum working electrode (BAS) was polished with BAS polishing alumina suspension and rinsed with acetone before use. The counter electrode was a platinum wire (BAS). The measured potentials were recorded with respect to the $Ag/AgNO_3$ (1.0×10^{-2} mol dm^{-3}) reference electrode. The E^0_{ox} values (*vs.* Ag/Ag^+) are converted into those *vs.* SCE by addition of 0.29 V.[18]

Results and Discussion

Reduction of NAD^+ by 2-Nitropropane Anion.—The lithium salt of 2-nitropropane is sparingly soluble in MeCN. No reaction occurred between the lithium salt of 2-nitropropane anion and a typical NAD^+ model compound, 1-benzylnicotinamidinium ion (BNA^+) in deaerated MeCN at 298 K. Upon mixing of the tetramethylammonium salt of 2-nitropropane anion instead of the lithium salt with BNA^+ in deaerated MeCN at 298 K, however, the absorption band due to BNA^+ (λ_{max} = 264 nm) disappeared, accompanied by the appearance of new absorption band (λ_{max} = 315 nm) with distinct isosbestic points as shown in Fig. 1. Such clear spectral changes were also observed in the reactions of 2-nitropropane anion with other

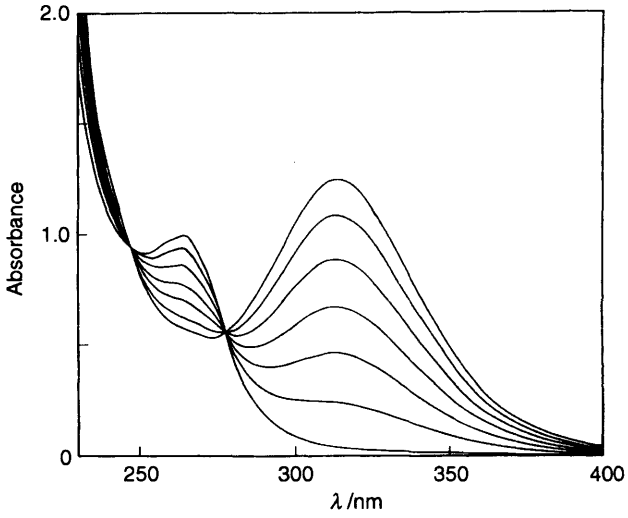


Fig. 1 Electronic absorption spectra observed in the reduction of $BNA^+ClO_4^-$ (2.1×10^{-3} mol dm^{-3}) by the tetramethylammonium salt of 2-nitropropane anion (0, 4.1×10^{-4}, 8.1×10^{-4}, 1.2×10^{-3}, 1.6×10^{-3}, 2.0×10^{-3} and 2.4×10^{-3} mol dm^{-3}) in deaerated MeCN at 298 K

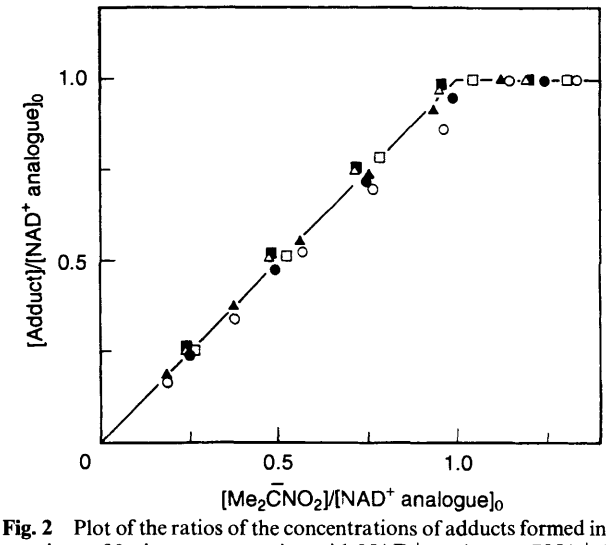
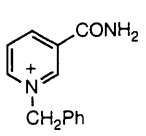
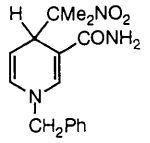
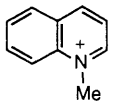
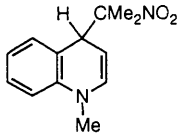
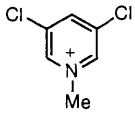
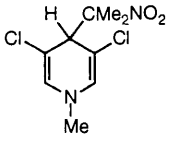
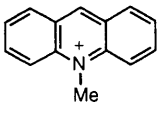
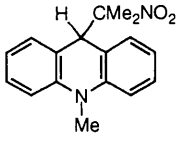


Fig. 2 Plot of the ratios of the concentrations of adducts formed in the reactions of 2-nitropropane anion with NAD^+ analogues: BNA^+ (○); QuH^+ (●); 3-$CNQuH^+$ (△); 3-$BrQuH^+$ (▲); 2-$MeQuH^+$ (□) and $AcrH^+$ (■) to the initial concentration of NAD^+ analogues (2.1×10^{-3} mol dm^{-3}), $[Adduct]/[NAD^+ analogue]_0$ *vs.* the ratios of the concentrations of 2-nitropropane anion to the initial concentration of NAD^+ analogues, $[Me_2\bar{C}NO_2]/[NAD^+ analogue]_0$ in deaerated MeCN

NAD^+ analogues [1-methylquinolinium ion derivatives (X-QuH^+: X = H, 2-Me, 3-Br and 3-CN), 3,5-dichloro-1-methylpyridinium ion ($3,5\text{-}Cl_2PyH^+$) and 10-methylacridinium ion ($AcrH^+$)]. The stoichiometry was established by spectral titration as shown in Fig. 2, where one 2-nitropropane anion reacts with one NAD^+ analogue to yield the product. The products were identified as the 2-nitropropane adducts of NAD^+ analogues by the ^1H NMR spectrum (see the Experimental section) and the yields are listed in Table 1, together with the one-electron reduction potentials (E^0_{red}) of NAD^+ analogues,[10–12] which are a measure of the oxidizing ability of NAD^+ analogues. An important point to note from Table 1 is that the addition of 2-nitropropane anion to various NAD^+ analogues of different oxidizing ability is always highly regioselective, yielding exclusively the corresponding 1,4-adducts and that no 1,2- (or 1,6-adduct in the case of BNA^+) is formed. Such selective 1,4-adduct formation in the reactions of BNA^+ [eqn. (1)] and QuH^+ [eqn. (2)] is in sharp contrast with the

Table 1 Reduction of NAD^+ analogues (1.0×10^{-1} mol dm^{-3}) by the tetramethylammonium salt of 2-nitropropane anion (1.2×10^{-1} mol dm^{-3}) and the one-electron reduction potentials (E°_{red}) of NAD^+ analogues in deaerated acetonitrile at 298 K

NAD^+ analogue	E°_{red}/V *vs.* SCE[a]	Product yield (%)
		
BNA^+	-1.08	1,4-BNA(CMe_2NO_2) (100)
		
QuH^+	-0.96	1,4-QuH(CMe_2NO_2) (100)
2-MeQuH^+	-1.05	2-Me-1,4-QuH(CMe_2NO_2) (100)
3-BrQuH^+	-0.76	3-Br-1,4-QuH(CMe_2NO_2) (100)
3-CNQuH^+	-0.60	3-CN-1,4-QuH(CMe_2NO_2) (100)
		
3,5-Cl_2PyH^+	-	3,5-Cl_2-1,4-PyH(CMe_2NO_2) (100)
		
$AcrH^+$	-0.43	AcrH(CMe_2NO_2) (100)

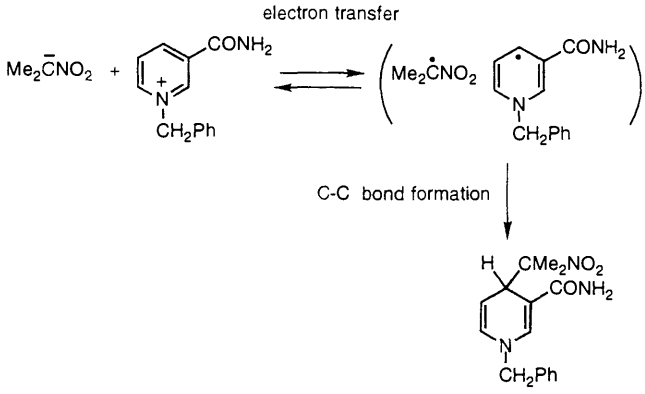
[a] Taken from ref. 11.

reductive methylation of BNA^+ [eqn. (3)] and QuH^+ [eqn. (4)] by *trans*-dimethylcobalt(III) complex, *trans*-[CoMe(L)] (L = 11-hydroxy-2,3,9,10-tetramethyl-1,4,8,11-tetraazaundeca-1,3,8,10-tetraen-1-olate); the former yields a mixture of 1,6-, 1,4- and 1,2-adducts, and the latter yields the 1,2-adduct selectively.[11]

It has been reported that in the case of the reaction of methoxide ion with 5-bromo-3-methoxycarbonylpyridinium ion the initial attack occurred at the 6-position to yield the 1,6-adduct which subsequently rearranged to give the 1,4-adduct.[2a] In the present case, however, no isomerization was observed as demonstrated by the presence of clean isosbestic points in Fig. 1. In order to confirm this point the time course of the reaction of 2-nitropropane anion with BNA^+ in deaerated MeCN at 298 K was monitored by stopped-flow spectrophotometry. However, the reaction was too fast to determine the rates accurately. The limit of the second-order rate constant (k_{obs}) was estimated to be $> 1 \times 10^6$ dm^3 mol^{-1} s^{-1} (see the Experimental section). The same minimum k_{obs} values were obtained for the reactions of 2-nitropropane anion with other NAD^+ analogues (X-QuH^+, 3,5-Cl_2PyH^+ and $AcrH^+$). A fast isomerization equilibrium[2a,19] is unlikely to occur in the present case, since the isomerization of dihydroquinolines is known to occur very slowly.[11,20]

In order to compare the thermodynamic stability of the different isomers the Δ_fH (heat of formation) values of the 1,2-, 1,4- and 1,6-isomers were calculated by using the PM3 method[16] with the geometrical parameters optimized. The optimized structures of the isomers and the Δ_fH values are shown in Fig. 3, where the 1,6-isomer was found to be the most stable. Thus, the selective formation of the 1,4-isomer may be kinetically controlled and no isomerization to the 1,6-isomer takes place.

Katritzky *et al.*[21,22] have reported that *C*-alkylation of the sodium salt of 2-nitropropane anion by *N*-substituted pyridinium ions proceeds by electron transfer from 2-nitropropane anion to *N*-substituted pyridinium ions. If such an electron transfer mechanism is also operative in the reactions of 2-nitropropane anion with NAD^+ analogues, the selective formation of the 1,4-isomer may be explained by Scheme 1, where



Scheme 1

the electron transfer from $Me_2\bar{C}NO_2$ to BNA^+ gives the radical pair ($Me_2\dot{C}NO_2BNA^\bullet$). The C–C bond formation in the radical pair is expected to occur at C-4 where the spin density is known to be greatest.[11] In order to evaluate the contribution of such an electron transfer pathway it was essential to determine the one-electron oxidation potential (E°_{ox}) of 2-nitropropane anion in MeCN. The E°_{ox} value of the sodium salt of 2-nitropropane anion has been reported to be 0.59 V (*vs.* SCE) in a footnote in Katritzky's paper,[21] although no details are given. The validity of the E°_{ox} value of 2-nitropropane anion has been questioned by Eberson[23] who pointed out that E°_{ox} should be more negative than 0.59 V judging from the well established $S_{RN}1$ behaviour, with electron transfer from 2-nitropropane anion to 4-nitrobenzyl bromide comprising the initiation step. In addition, the E°_{ox} value of the tetramethylammonium salt of 2-nitropropane anion is expected to be more negative than that of the sodium salt, since the former is known to be far more reactive than the corresponding lithium or sodium salt, in which the metal ion forms a strong ion pair.[24] Thus, we have determined the E°_{ox} value of the tetramethylammonium salt of 2-nitropropane anion by analysing the cyclic voltammograms (*vide infra*).

One-electron Oxidation Potential of 2-Nitropropane Anion.— The cyclic voltammograms of 2-nitropropane anion show well-defined anodic waves but no corresponding cathodic waves on the reverse scan, as shown in Fig. 4. The transfer coefficient β defined by the tangent of the Gibbs energy change of electron transfer at the anodic peak potential is obtained from the width of the wave $E^P_{ox} - E_{ox}{}^{P/2}$ by using eqn. (5).[25] On the other hand,

$$\beta = 1.857RT/[F(E^P_{ox} - E_{ox}{}^{P/2})] \quad (5)$$

the transfer coefficient β is given as a function of the Gibbs energy change of electron transfer (ΔG°_{et}) by using Marcus theory, eqn. (6), where $\Delta G^\ddagger_0$ is the activation Gibbs energy of

$$\beta = (1/2) + \Delta G^\circ_{et}/(8\Delta G^\ddagger_0) \quad (6)$$

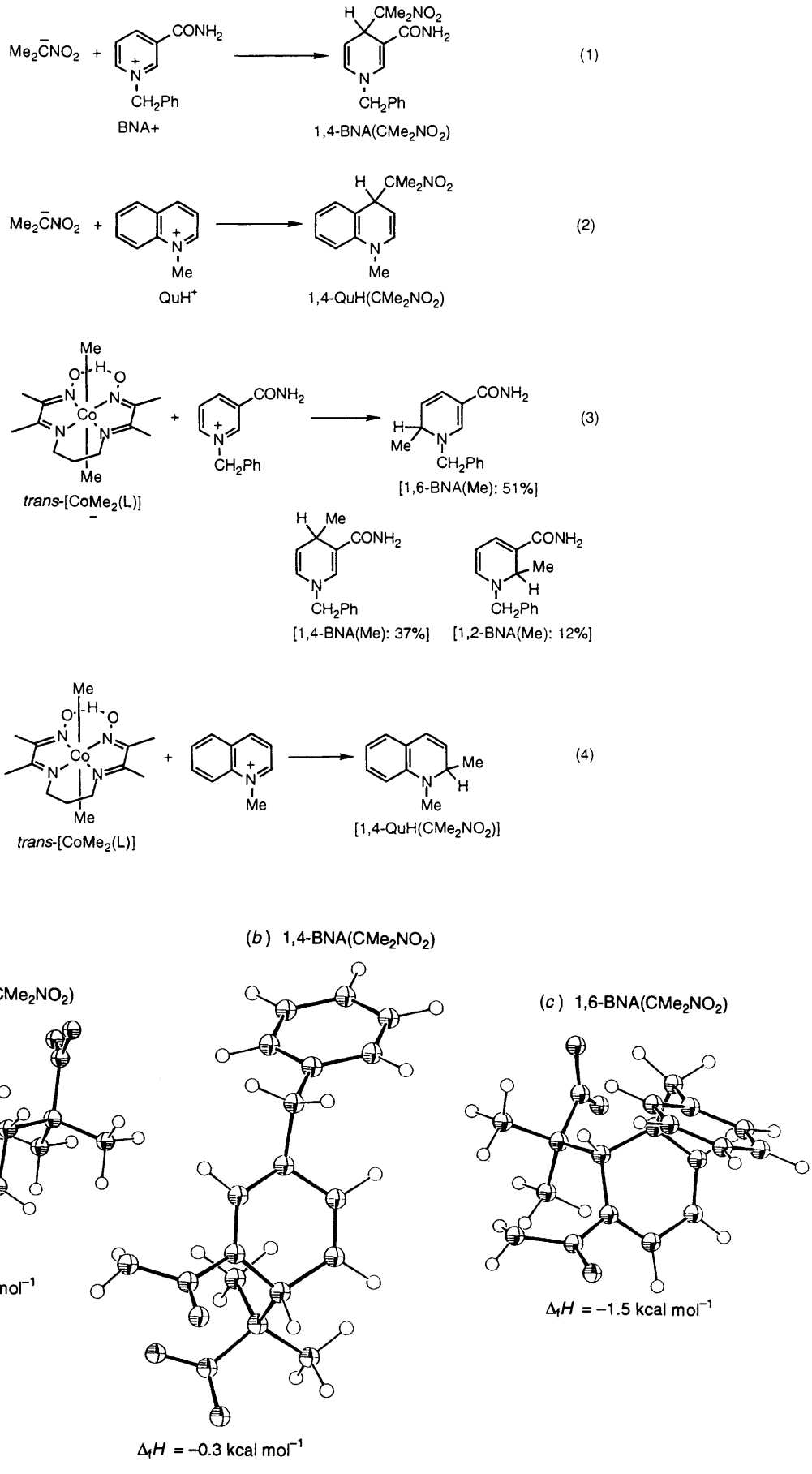


Fig. 3 Optimized structures of the isomers of 2-nitropropane anion adduct of BNA^+, (*a*) 1,2-BNA(CMe_2NO_2), (*b*) 1,4-BNA(CMe_2NO_2), (*c*) 1,6-BNA(CMe_2NO_2), and the values of the heats of formation Δ_fH, calculated by using the PM3 method

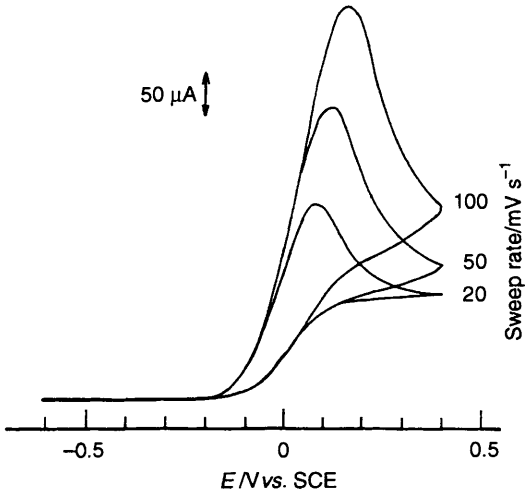


Fig. 4 Cyclic voltammograms of 2-nitropropane anion (1.1×10^{-2} mol dm^{-3}) in the presence of $NBu^n_4ClO_4$ (5×10^{-2} mol dm^{-3}) in deaerated MeCN at different sweep rates

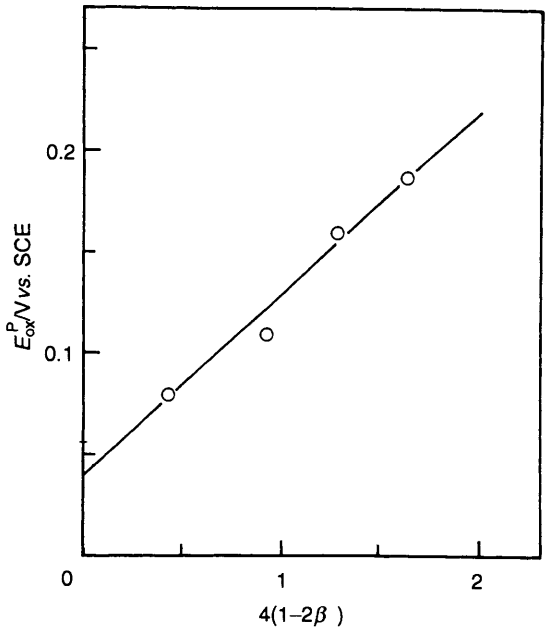


Fig. 5 The oxidation peak potential E^P_{ox} of 2-nitropropane anion in deaerated MeCN at 298 K plotted as a function of transfer coefficient β, $4(1 - 2\beta)$, see eqn. (7)

activation at $\Delta G^\circ_{et} = 0$.[26] Since $\Delta G^\circ_{et} = E^\circ_{ox} - E^P_{ox}$, the relationship between E^P_{ox} and E°_{ox} [eqn. (7)] can be derived from

$$E^P_{ox} = E^\circ_{ox} + 4(1 - 2\beta)\Delta G^\ddagger_0 \qquad (7)$$

eqns. (5) and (6).[10–12] Both the E^P_{ox} and $E^P_{ox} - E_{ox}{}^{P/2}$ values vary depending on the sweep rate, as shown in Fig. 4. The E^P_{ox} values at various sweep rates were then plotted *vs.* $4(1 - 2\beta)$ in Fig. 5, where the β values were obtained from $E^P_{ox} - E_{ox}{}^{P/2}$ by using eqn. (5). The linear correlation in Fig. 5 agrees well with eqn. (7). Thus, from intercept of the linear plot, the E°_{ox} value of 2-nitropropane anion was determined to be 0.04 V. The $\Delta G^\ddagger_0$ value in the one-electron oxidation of 2-nitropropane anion was also determined to be 2.1 kcal mol^{-1} from the slope by using eqn. (7).

It may be suspected, however, that the observed changes in E^P_{ox} are due, in part at least, to the coupling of the electron transfer to the follow-up chemical reaction. We have also SHACV to obtain the E°_{ox} value, since the SHACV method is known to provide a superior approach to the direct evaluation of the one-electron redox potentials in the presence of a follow-up chemical reaction, relative to the better-known dc and fundamental harmonic ac methods.[13] The well-defined symmetrical SHACV trace was obtained for the one-electron oxidation of the tetramethylammonium salt of 2-nitropropane anion in MeCN as shown in Fig. 6(*a*). An E°_{ox} value, determined from the intersection with the dc potential axis at the phase angle where two SHACV lobes are symmetrical, has recently been reported to be more negative than the actual standard potential.[27] In the present case, however, the sharply delineated E°_{ox} value of −0.19 V (*vs.* Ag/Ag$^+$), which is converted into 0.10 V (*vs.* SCE),[18] agrees well with the estimated value from the analysis of the sweep-rate dependence of CV peak potentials. A SHACV trace was also obtained for the Li$^+$ salt of 2-nitropropane anion in DMSO as shown in Fig. 6(*b*), since it is barely soluble in MeCN. The E°_{ox} value (*vs.* SCE) of the Li$^+$ salt (0.48 V) in Fig. 6(*b*) is 0.38 V more positive than that of the tetramethylammonium salt in Fig. 6(*a*) as expected from the strong ion-pair formation of the Li$^+$ salt. The slightly higher E°_{ox} value (0.59 V) of the Li$^+$ salt of 2-nitropropane anion reported previously, compared with the E°_{ox} value determined directly with the SHACV method in Fig. 6(*b*) may be ascribed to insufficient correction for the irreversible nature in the one-electron oxidation.

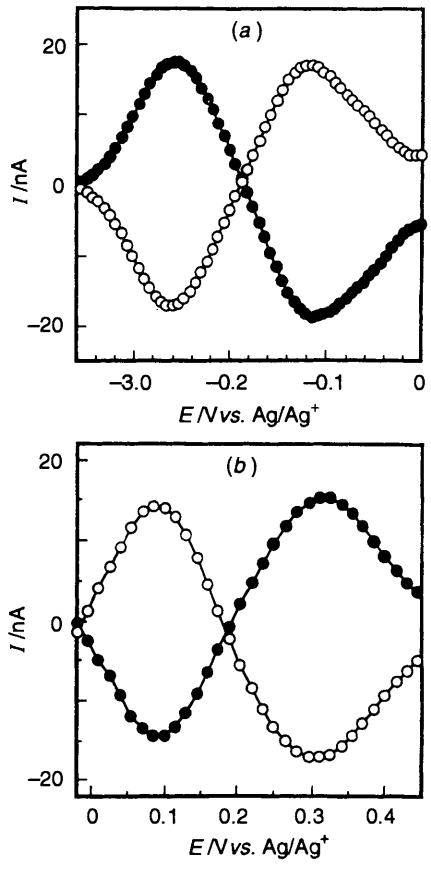


Fig. 6 Reversible second-harmonic ac voltammograms for the one-electron oxidation of (*a*) the tetramethylammonium salt of 2-nitropropane anion (1.0×10^{-2} mol dm^{-3}) in MeCN; ac amplitude 25 mV, frequency 50 Hz, scan rate 4 mV s^{-1}, phase angle 88° (○), 178° (●), and (*b*) the lithium salt of 2-nitropropane anion (5.0×10^{-3} mol dm^{-3}) in DMSO; ac amplitude 50 mV, frequency 50 Hz, scan rate 10 mV s^{-1}, phase angle 7° (○), 98° (●)

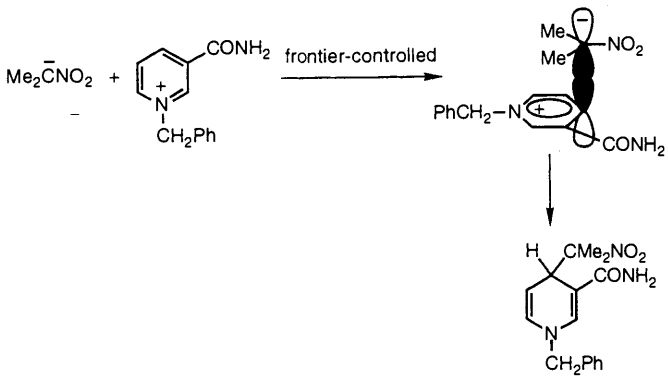
Mechanism of Selective 1,4-*Addition of* 2-*Nitropropane Anion with NAD*$^+$ *Analogues.*—Judging from the E°_{ox} value of 2-nitropropane anion (0.10 V) and the E°_{red} value of BNA$^+$ (−1.08 V),[10] the electron transfer from 2-nitropropane anion to BNA$^+$ is highly endergonic; the Gibbs energy change $\Delta G^\circ_{et} =$ 114 kJ mol^{-1}. In such a highly endergonic electron transfer reaction, the maximum value of the electron transfer rate constant

(k_{et}) may be obtained by using eqn. (8), in which Z is the

$$k_{et} = Z \exp[-F(E^{\circ}_{ox} - E^{\circ}_{red})/RT] \quad (8)$$

collision frequency, taken as 1×10^{11} dm^3 mol^{-1} s^{-1}, and F is the Faraday constant.[11] The k_{et} value obtained was 1.1×10^{-9} dm^3 mol^{-1} s^{-1}, which is at least 10^{15} times smaller than the observed value ($k_{obs} > 1 \times 10^6$ dm^3 mol^{-1} s^{-1}). Such a large discrepancy between the k_{obs} and k_{et} values clearly excludes an outer-sphere electron-transfer pathway. The discrepancy would be larger if the E°_{ox} value determined by SHACV was the lowest limit.[27]

The drastic change in the regioselectivity depending on the nature of nucleophile may be explained in terms of the HSAB (hard and soft acids and bases) principle.[28] The hard nucleophiles (low-energy HOMO) are expected to react faster at the 2-position, which is harder than the 4-position.[29] According to the orbital interactions the hard–hard reaction is fast because of a large coulombic attraction. Since the E°_{ox} value of *trans*-[$CoMe_2(L)$] (0.53 V) is more positive than that of 2-nitropropane anion (0.10 V), the former nucleophile is harder than the latter. This may be the reason why *trans*-[$CoMe_2(L)$] reacts with BNA^+ at the 6-position predominantly [eqn. (3)] and X-QuH^+ at the 2-position selectively [eqn. (4)]. On the other hand, the softer nucleophile, *i.e.*, 2-nitropropane anion, attacks the 4-position selectively, since the softer nucleophiles react faster at the 4-position which is softer than the 2- or 6-position. Such a soft–soft reaction is favoured because of a large orbital interaction between the HOMO of 2-nitropropane and the LUMO of the 4-position of NAD^+ analogues, where the atomic coefficient is the largest,[11] as shown in Scheme 2. Thus, the



Scheme 2

reactions of 2-nitropropane with NAD^+ analogues may be frontier-orbital controlled to yield the 1,4-adduct selectively.

Acknowledgements

This work was supported in part by a grant-in-aid for scientific research from the Ministry of Education, Science and Culture, Japan.

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Paper 4/00257A
Received 17*th January* 1994
Accepted 5*th April* 1994