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Syntheses and Redox Behavior of Novel Cyclic Hosts Having Multiple Redox Centers of NAD$^+$ Analogue

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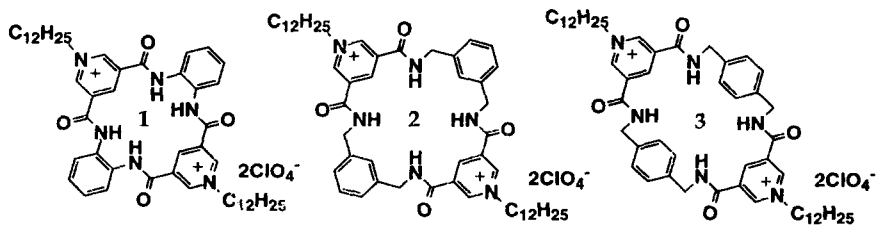
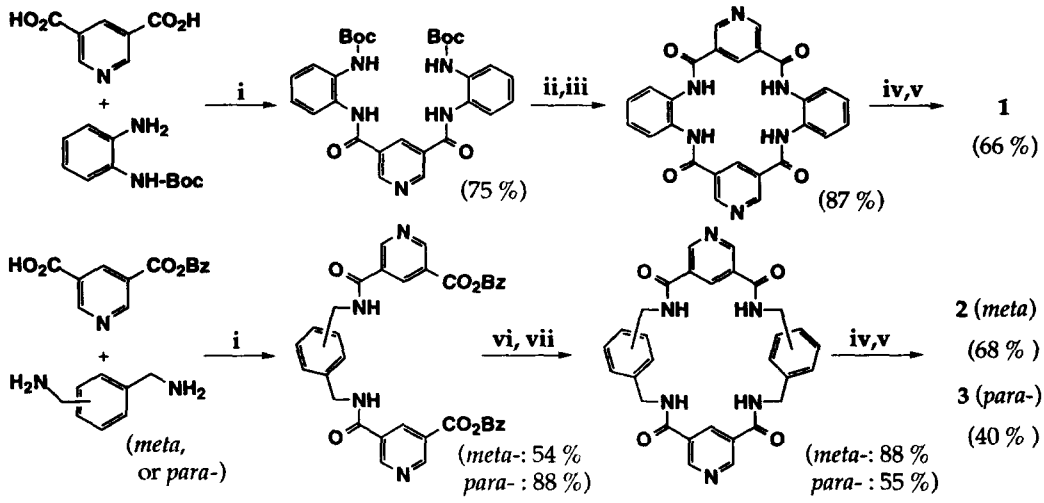
Abstract; *A new series of cyclophanes having 3,5-dicarbamoylpyridinium moieties were synthesized by the stepwise reactions starting from half protected compounds. The one-electron reduction potentials of these new cyclophane type NAD$^+$ analogues are determined by the cyclic voltammetric method. The results indicate that the reduction potentials are primarily regulated by the through-bond mechanism.*

Cyclophanes have been providing interesting artificial recognition sites in host-guest chemistry. Various types of cyclophanes have been synthesized and examined as artificial inclusion host molecules having specific binding sites surrounded with aromatic π-electron walls.[1] Among the aromatic rings used for these cyclophanes, N-alkylnicotinamide analogues are a unique class of cyclophane components, because of their NADH-like redox activities and cationic character. Several cyclophanes containing N-alkylnicotinamide analogues in their basic skeletons have been synthesized as reductase models which specifically bind and reduce substrates.[2] In spite of these interesting chemical reactivities of these reductase mimics, their physical properties such as redox potentials are little investigated. We report here syntheses and redox behavior of new series of cyclophanes having two NAD$^+$ analogous moieties in their main frameworks. The redox potentials described in this article are the first example of electrochemically determined reduction potentials of cyclophane type NAD$^+$ analogues.

We designed three types of new cyclophanes, **1**, **2** and **3**, consisting of two 3,5-dicarbamoyl-pyridinium rings which have *n*-dodecyl chains for solubilization into organic solvents. The spacer moieties employed are *o*-phenylenediamine for **1** and *m*- and *p*-xylylenediamine for **2** and **3**. The distances between two C_4 atoms of pyridinium rings of these cyclophanes are estimated to be 5.3 Å for **1** , 8.5 Å for **2**, and 8.8 Å for **3** by computer modeling. [3]





Scheme 1. **i**: BOP/Et_3N in DMF at r.t. for 24 h. **ii**: TFA in CH_2Cl_2 at r.t. for 3 h. **iii**: 3,5-pyridine-dicarboxylic acid, BOP/Et_3N in DMF at r.t. for 24 h. **iv**: *n*-$C_{12}H_{25}Br$ in DMF at 80 °C for a week. **v**: $AgClO_4$ in DMF at r.t. for 12 h. **vi**: NaOH aq. in DMF at r.t. for 1~4 days, **vii**: *m*, or *p*-xylylenediamine, BOP/Et_3N in DMF at r.t. for 24 h.

The synthetic routes for these cyclophanes are shown in Scheme 1. Since direct one-pot cyclization reactions using 3,5-pyridinedicarboxylic acid and corresponding diamino components gave no appreciable amount of desired products, the present cyclophanes were prepared by the stepwise reactions starting from half protected compounds. For syntheses of **2** and **3**, half protected 3,5-pyridine-dicarboxylic acid was used in the first condensation steps in order to avoid exposure of free benzylamine moiety in the intermediates which is relatively unstable for oxidation during purification procedures. The spectroscopic and elemental analysis data of final cyclophanes showed good agreement with those expected for the corresponding structures. [4]

The quantitative redox properties of NAD^+/NADH analogues have been somewhat ambiguous due to their character as two electron carriers which sometimes result in irreversibility of each elemental reduction. Since the first one-electron reduction potentials of the present compounds are interesting not only as the first examples of these values for cyclophane type NAD^+ analogues but also as information on the redox behavior of intramolecular multi-cationic redox centers, we attempted to determine the reduction potentials by the cyclic voltammetric method which was developed by Fukuzumi *et al.* for irreversible systems including NAD^+/NADH analogues. [5] The first one-electron reduction potential E° is determined based on the following relationship;

$$E^p = E^\circ - 4\,(1 - 2\beta)\,\Delta G_0^{\ddagger}$$

where E^p and $\Delta G_0^{\ddagger}$ are the observed cathodic peak potential and the self-exchange activation energy in the Marcus theory, respectively. The transfer coefficient β is given by

$$\beta = 1.857RT / F\,(E^{p/2} - E^p)$$

where F and $E^{p/2}$ are the Faraday constant and the observed half peak potential, respectively.

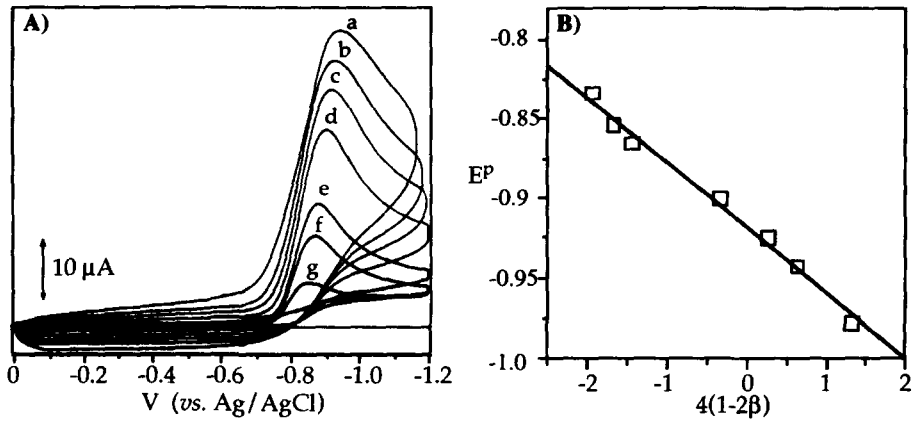


Figure 1. A) Cyclic voltammograms of **1** in DMF containing 0.1M n-Bu_4NClO_4 at sweep rates of (a)1000, (b) 700, (c) 500, (d) 300, (e) 100 , (f) 50, (g) 10 mV/sec. B) the plot of E^p *vs.* 4(1-2β).

The typical results of cyclic voltammetric measurements for **1** at various sweep rates are shown in Figure 1A. The value of E° of **1**, -0.93V (*vs.* Ag/AgCl), is obtained as the intercept of the plot of E^p *vs.* 4 (1 - 2β) shown in Figure 1B. In all cases examined in this work, similar excellent linear relationships between E^p and 4 (1 - 2β) were observed. The reduction potentials of the present cyclophanes similarly determined are summarized in Table 1 together with those of monomeric diamide, **4** and **5**. [6]

Interestingly, cyclophanes **2** and **3** show the practically same reduction potential with that of the corresponding monomer **5**. The results indicate that two cationic pyridnium moieties in **2** and **3** are reduced independently and show no specific interaction between them. In contrast, the reduction potential of **1** (-0.93 V) is slightly higher than that of the corresponding monomer **4** (-0.97 V). There are two possible explanations for these observations, *i.e.*, a) through-space repulsion between closely packed two cationic centers of **1** within much shorter distance compared with **2** or **3**, b) a through-bond effect through partially conjugated phenylenediamide spacers of **1**. Further insights into the reduction potentials of multi-pyridinium systems have come from investigation of a new cyclophane **6** which we preliminarily prepared. Although this trimeric cyclophane has

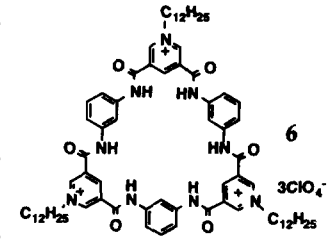


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Table 1. One-electron reduction potentials of NAD^+ analogues determined in this work.

Compound	1	2	3	PhHNOC, CONHPh, ClO_4^-, Me **4**	BzHNOC, CONHBz, ClO_4^-, Me **5**
E° (V)[a]	-0.93	-1.00	-0.99	-0.97	-1.00

a) *vs.* Ag/AgCl (3 M NaCl) in DMF containing 0.1M n-Bu_4NClO_4 at r.t.. A glassy carbon electrode was used as a working electrode. The experimental errors are within ± 0.03 V.

m-phenylene-diamine spacers which keep the pyridinium moieties at longer distance (9.7 Å), its reduction potential is found to be practically same with that of **1** (-0.93 V). The observation strongly suggests that the first one-electron reduction potentials of the present NAD^+ analogues are primarily regulated by the through-bond mechanism.

References and Notes.

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3. The molecules were optimized on Spartan (Wavefunction Inc.) by using AM-1 method.
4. **1**: ^1H NMR in DMSO-d_6 (500 MHz, referenced to residual protons of DMSO-d_6 at 2.49 ppm) δ 10.51 (s, 4H, amide NH), 9.73 (apparent s, 4H, pyridine $H_{2,6}$), 9.62 (apparent s, 2H, pyridine H_4), 7.92 (apparent dd, J = 3.7, 5.5 Hz, 4H, phenylene), 7.46 (apparent dd, J = 3.7, 5.8 Hz, 4H, phenylene), 4.80 (t, J = 7.5 Hz, 4H, N^+CH_2), 1.97-2.07 (m, 4H, $N^+CH_2\underline{CH_2}$), 1.37-1.18 (m, 36H, the rest of CH_2), 0.84 (t, J = 6.9 Hz, 6H, terminal CH_3). HRMS (FAB) m/z [$(M\text{-}ClO_4^-)^+$ = $C_{50}H_{68}N_6O_8{}^{35}Cl$] calcd 915.4787, obsd 915.4840. *Anal.* calcd for $C_{50}H_{68}N_6O_{12}Cl_2$ (MW 1016.04): C, 59.11; H, 6.75; N, 8.27. found: C, 59.03; H, 6.66; N, 8.35. **2**: ^1H NMR in DMSO-d_6 (500 MHz) δ 9.67 (t, J = 5.5 Hz, 4H, amide NH), 9.58 (d, J = 1.5 Hz, 4H, pyridine $H_{2,6}$), 9.17 (t, J = 1.5 Hz, 2H, pyridine H_4), 7.28-7.36 (m, 8H, xylylene benzene), 4.67 (t, J = 7.6 Hz, 4H, N^+CH_2), 4.50 (d, J = 5.5 Hz, 8H, xylylene CH_2), 1.90-2.00 (m, 4H, $N^+CH_2\underline{CH_2}$), 1.34-1.20 (m, 36H, the rest of CH_2), 0.84 (t, J = 7.0 Hz, 6H, terminal CH_3). HRMS (FAB) m/z [$(M\text{-}ClO_4^-)^+$ = $C_{54}H_{76}N_6O_8{}^{35}Cl$] calcd 971.5413, obsd 971.5521. *Anal.* calcd for $C_{54}H_{76}N_6O_{12}Cl_2$ (MW 1072.15): C, 60.50; H, 7.14; N, 7.84. found: C, 60.12; H, 7.13; N, 7.83. **3**: ^1H NMR in DMSO-d_6 (500 MHz) δ 9.55 (d, J = 1.5 Hz, 4H, pyridine $H_{2,6}$), 9.51 (t, J = 5.8 Hz, 4H, amide NH), 9.02 (t, J = 1.5 Hz, 2H, pyridine H_4), 7.31 (s, 8H, xylylene benzene), 4.70 (t, J = 7.5 Hz, 4H, N^+CH_2), 4.49 (d, J = 5.8 Hz, 8H, xylylene CH_2), 1.92-2.02 (m, 4H, $N^+CH_2\underline{CH_2}$), 1.34-1.20 (m, 36H, the rest of CH_2), 0.84 (t, J = 7.0 Hz, 6H, terminal CH_3). HRMS (FAB) m/z [$(M\text{-}ClO_4^-)^+$ = $C_{54}H_{76}N_6O_8{}^{35}Cl$] calcd 971.5413, obsd 971.5500.
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6. The weak interactions between two pyridinium moieties of **1** - **3** possibly indicate that both moieties are reduced at the same potential. In any case, the observed potentials are considered to be that of the first one electron reduction for one pyridinium moiety to give radical species (not anion radical) as the product, though the second potential can not be detected by the present method due to the irreversibility of the processes, see ref. 5.

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