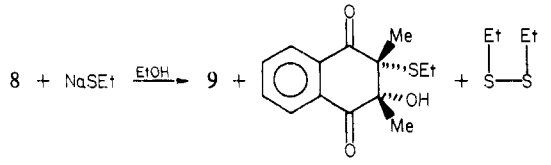
isomer of **8** (**10**). None of **10** was observed in the acid-catalyzed



10

reactions either in the presence or absence of ethanethiol. Another product in the reaction was identified by gas chromatography as diethyl disulfide and represents a model for the formation of the oxidized enzyme (**6** → vitamin K) in Scheme I. When compound **10** was treated with sodium ethylthiolate in ethanol for 15 min, 71% of the starting material reacted, and two new aromatic compounds were isolated. These two compounds were identified as **9** (62%) and **8** (38%) by comparison of their IR spectra with those of the authentic compounds. This indicates that the two isomers, **8** and **10**, are interconvertible under basic conditions,[22] and both produce naphthoquinone **9**. The mechanism for the interconversion of **8** and **10** was determined[23] to involve a retro-aldol–aldol condensation via **11** (pathway b, Scheme II) rather than thiol reduction to **12** (pathway a, Scheme II) followed by attack of **12** on the newly formed disulfide. However, the conversion of **8** or **10** to **9** under basic conditions could proceed either directly to **12** or via **11**. Oki et al.[24] have shown that β-keto sulfides (such as **6** or **11**) are reduced by thiols to ketones, presumably via the corresponding enolate. Since **8** also is converted to **9** in trifluoroacetic acid (vide supra) and no **10** is produced,[25] both routes (via **11** or directly to **12**) may be feasible depending upon conditions. Although Scheme I depicts direct sulfide reduction and elimination (**6** → vitamin K), the pathway which seems to be favored in acid, the ring cleavage pathway via **11**, which is favored in base,[23] also is a possibility. If this is the case, rather than enzyme-catalyzed proton donation to the hydroxyl group (**5** → **6**) an enzyme-catalyzed deprotonation of the hydroxyl would be required. The interconversion of **8** and **10** is probably not relevant to the enzyme model since the sulfide linkage formed would be to the enzyme and isomerization would be sterically difficult.

The observation that **8** does not undergo reaction at room temperature with ethanethiol and triethylamine in acetonitrile but rapidly reacts with sodium ethylthiolate in ethanol to give **9** can be rationalized on the basis of a difference in the nucleophilicity (and basicity[23]) of the anions[26] and as a solvent effect.[27] In accordance with the enhanced nucleophile (base) rationalization,[26] when **8** was treated with ethanethiol and triethylamine in ethanol at room temperature, no reaction took place in 5.5 h. Since **8** and **10** are rapidly converted to naphthoquinone **9** by sodium ethylthiolate in ethanol, the sodium salt must be a more powerful nucleophile than the triethylammonium salt.[26] Furthermore, the reaction of **8** or **10** with sodium ethylthiolate in acetonitrile leads to no reductive desulfuration[23] unlike the rapid reaction to give **9** in ethanol. Formation of enolate **12** and elimination of hydroxide apparently is favored in the hydroxylic solvent.[27]

A second reasonable enzymatic mechanism can be excluded on the basis of the results described here. Sulfhydryl attack could occur at one of the vitamin K epoxide carbonyl groups to give a hemithioketal. Attack of this α-hydroxy sulfide by thiolate with concomitant epoxide ring opening followed by enol tautomerization and hydroxide elimination also would give the naphthoquinone. However, the intermediate that was isolated contains *two* carbonyl groups;[12,13] only one carbonyl would be observed if hemithioketal formation were important. The model studies in this communication therefore provide chemical support for the mechanism of vitamin K epoxide reductase in Scheme I.

(21) IR (film) 3480 (s), 1698 (s), 1683 (s), 1592 (m), 1443 (m), 1265 (s) cm^{-1}.

(22) No evidence for this interconversion has been found under acidic conditions starting from either isomer.

(23) Silverman, R. B. *J. Org. Chem.* **1981**, *46*, in press.

(24) Oki, M.; Funakoshi, W.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 828.

(25) When **10** was treated with ethanethiol in trifluoroacetic acid for 26 h, **9** was produced only in a 2% yield. Since the yield of **9** is 40 times greater under the same conditions starting from **8**, it appears that the ethylthio substituent in **8** is axial to the carbonyl and that either a concerted reductive elimination (**6** → vitamin K) or a reductive E1cb elimination is possible. This also confirms the structure of **8** as the isomer with the sulfide and hydroxyl groups anti, as shown.

(26) The thiolate generated by the reaction of EtSH and Et_3N will be in low concentration because of the greater pK_a of EtSH than Et_3NH^+. Also, the thiolate produced under these conditions probably will be hydrogen bonded to Et_3NH^+ and should have different nucleophilic and basic properties than those of NaSEt.

(27) The enolate formed by thiolate attack on any of the β-hydroxy sulfides (**8**, **10**, **11**) would be stabilized in the hydroxylic solvent as compared with acetonitrile. Similarly, the pK_a of H_2O in a hydroxylic solvent is much lower than in a nonhydroxylic solvent;[28] therefore elimination of hydroxide from **12** to give the naphthoquinone in ethanol would be more favorable than in acetonitrile.

(28) (a) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295. (b) Bordwell, F. G.; Branca, J. C.; Hughes, D. L.; Olmstead, W. N. *Ibid.* **1980**, *45*, 3305.

Chelating Phosphinite Complexes of Group 6 Metal Carbonyls with Crown-Ether-Type Characteristics. Effect of Preferential Cation Binding on the Reactivity of Coordinated Carbon Monoxide

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Coordinated carbon monoxide may be activated with respect to alkyl/aryl migration (i.e., nucleophilic addition) and probably with respect to hydrogenation (methanation and "Fischer-Tropsch-type" synthesis) by formation of an adduct between a Lewis acid and a carbonyl oxygen in $L_nM(R)(CO)$ and/or by stabilization of the acyl product $L_nM(RCO{\rightarrow}A)$ (e.g., A = Li^+, $AlBr_3$, or Cp_2Zr^+).[1-7] We now report that *preferential cation binding by the product molecule* can be utilized to activate coordinated carbon monoxide toward nucleophilic additions.

The series of complexes *cis*-$(M(CO)_4[Ph_2P(OCH_2CH_2)_nOPPh_2])$ (complexes **1**; M = Cr, Mo, W; n = 2, 3, 4, 5) have been prepared in 20–70% yield from the reaction of the appropriate bis(diphenylphosphinite) ligand with $M(CO)_4$(norbornadiene) by using high dilution techniques. Complexes **1**, which have been fully characterized,[8] have structures suggesting potential crown ether reactivity. We have used ^{13}C NMR spectroscopy as a probe of crown-ether-type interactions between **1** (M = Mo) and the alkali metal cations.[9,10] These studies show that **1** (n = 5) will complex Li^+ and Na^+, **1** (n = 4) will complex Li^+ only (see Figure 1), and the ^{13}C chemical shifts of **1** (n = 3 or 2) are unaffected by the presence of group 1A cations (i.e., no or only weak complexation).

It is well-known that the carbonyl complexes $LM(CO)_5$ (L = CO, PR_3) will react with strong nucleophiles, such as MeLi, to

(1) Butts, S. B.; Strauss, S. H.; Holt, E. M.; Stimson, R. E.; Alcock, N. W.; Shriver, D. F. *J. Am. Chem. Soc.* **1980**, *102*, 5093 and references therein.

(2) Collman, J. P.; Finke, R. G.; Cawse, J. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1978**, *100*, 4766.

(3) Darensbourg, M. Y.; Barros, H. L. C. *Inorg. Chem.* **1979**, *18*, 3286 and references therein.

(4) Demitras, G. C.; Muetterties, E. L. *J. Am. Chem. Soc.* **1977**, *99*, 2796.

(5) Muetterties, E. L.; Stein, J. *Chem. Rev.* **1979**, *79*, 479.

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(7) Butts, S. B.; Richmond, T. G.; Shriver, D. F. *Inorg. Chem.* **1981**, *20*, 278.

(8) For example, Anal. Calcd for **1** (M = Mo), n = 2: C, 56.3; H, 4.1; M_r, 672. Found: C, 56.1; H, 4.0; M_r, 640. Calcd for n = 3: C, 56.2; H, 4.4; M_r, 726. Found: C, 56.0; N, 4.4; M_r, 754. Calcd for n = 4: C, 56.1; H, 4.7; M_r, 770. Found: C, 56.1; H, 4.6; M_r, 735. Calcd for n = 5: C, 56.0; H, 4.9; M_r, 814. Found: C, 55.8; H, 4.7; M_r, 800. Molecular weights determined osmometrically in $CHCl_3$.

(9) Lehn, J. M.; Sonveaux, E.; Willard, A. K. *J. Am. Chem. Soc.* **1978**, *100*, 4914.

(10) Shamsipur, M.; Popov, A. I. *J. Am. Chem. Soc.* **1979**, *101*, 4051.

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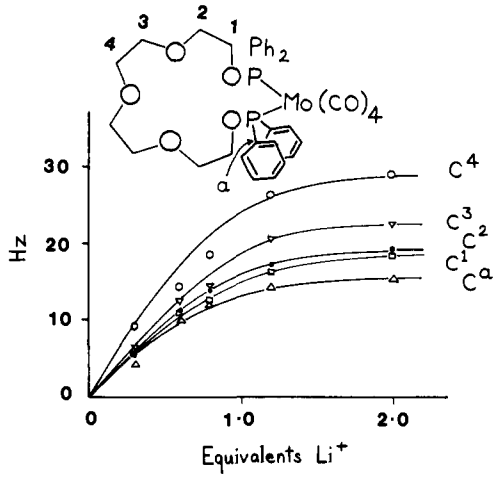


Figure 1. Plot of the change in $\delta^{13}C$ (Hz) vs. equivalents of added $LiPF_6$ for chelate ring and α-phenyl carbon nuclei of complex **1** (M = Mo, n = 4) (0.17 M solutions of **1** in $CDCl_3$, 34 °C).

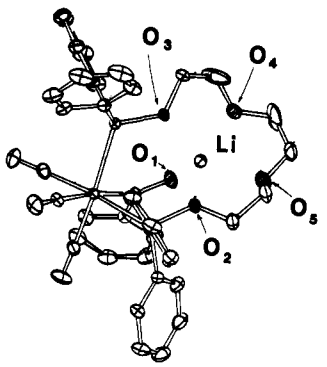
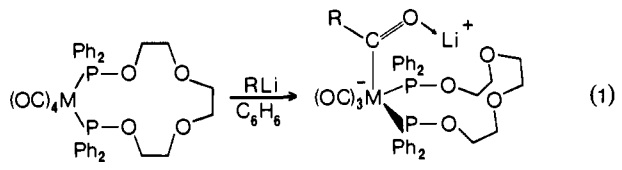


Figure 2. Molecular geometry of $(OC)_3Mo(PhCOLi)[Ph_2P(OCH_2CH_2)_3OPPh_2]$, complex **2** (M = Mo, R = Ph), as determined by X-ray crystallography. Bond lengths (Å) and angles (deg) about Li are Li–O_1, 1.84; Li–O_2, 2.09; Li–O_3, 2.00; Li–O_4, 2.20; LiO_5, 2.05; $\angle O_1LiO_2$, 103; $\angle O_1LiO_3$, 104; $\angle O_2LiO_3$, 103; $\angle O_1LiO_5$, 111; $\angle O_1LiO_4$, 118; $\angle O_2LiO_5$, 79; $\angle O_3LiO_4$, 78; $\angle O_4LiO_5$, 76.

give isolable lithium acylates $LM(CO)_4(MeCOLi)$.[11,12] In contrast there is no report in the literature of a similar reaction between *cis*-$M(CO)_4(PR_3)_2$ and RLi. Consistent with this we have found that the complexes *cis*-$Mo(CO)_4(PPh_2OMe)_2$ and complexes **1** (n = 2, 4, and 5) do not react to a significant extent with RLi (R = CH_3, Ph, *t*-Bu, Et_2N) even on addition of tetramethylethylenediamine (TMED).[13] In contrast complexes **1** (n = 3) react rapidly with RLi to give the complexes **2** as fully characterized yellow-orange crystalline solids in essentially quantitative yields (reaction 1).[14] The basic features of the molecular geometry



(1)

1 (n=3)

2 M = Cr, Mo, W
R = Me, Ph, ^{t}Bu, Et_2N

(11) Fischer, E. O. *Adv. Organomet. Chem.* **1976**, *14*, 1.
(12) Cardin, D. J.; Cetinkaya, B.; Lappert, M. F. *Chem. Rev.* **1972**, *72*, 545.
(13) Solution infrared studies indicate partial reaction in the presence of a large excess of RLi. On workup only starting material is recovered.
(14) For example, analytical and IR data for complex **2** (M = Mo, R = Ph). Anal. Calcd for $C_{40}H_{37}LiMoO_8P_2 \cdot CH_2Cl_2$: C, 54.75; H, 4.21. Found: C, 55.28; H, 3.85 (presence of 1 mol equiv of CH_2Cl_2 in crystal confirmed by X-ray structural study). ν_{CO} 1935 s, 1851 s, 1821 s cm^{-1} (terminal CO's); 1470 cm^{-1} (ν_{CO} of benzoylate).

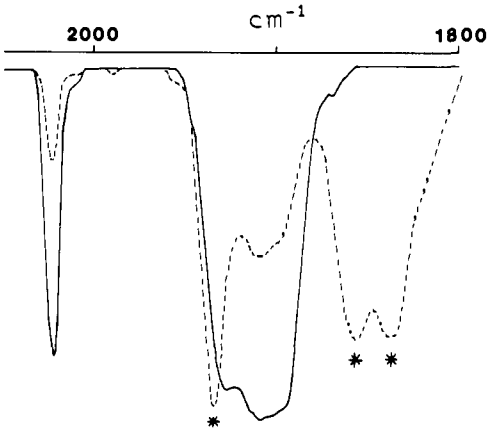


Figure 3. Infrared spectrum ν_{CO} region for a 7.25×10^{-3} M solution of complex **1** (M = Mo, n = 3) in THF, 25 °C (–); and infrared spectrum after addition of a 1 molar equiv of PhLi (---). Asterisk indicates adsorptions due to the benzoylate product **2** (M = Mo, R = Ph).

Table I. Infrared Data (ν_{CO} region) and Selected Equilibrium Constant Data [(K = $[Mo(CO)_3(PhCOLi)P_2]/([Mo(CO)_4P_2][PhLi])$] As Determined by Infrared Spectroscopy (ν_{CO} region) for Reaction 2 in THF and Benzene Solutions (7.25×10^{-3} M in Mo) at 25 °C

		equilibrium constants,[a] L mol^{-1}	
complex	ν_{CO}, cm^{-1}	$K(PhLi)_{THF}$	$K(PhLi)_{C_6H_6}$
1 (n = 2)	2025, 1933, 1912, 1898	<7	<45
1 (n = 3)	2024, 1928, 1909, 1899	2700	>100000
3	2023, 1931, 1906, 1899	50000	>300000
4	2022, 1929, 1908, 1894	90	1000
5a	2024, 1923, 1910, 1899	500	1100
5b	2016, 1915, 1901, 1887	250	
6a	2020, 1920, 1908, 1878	<0.01	<0.01
6b	2014, 1907, 1895, 1868	<0.01	<1

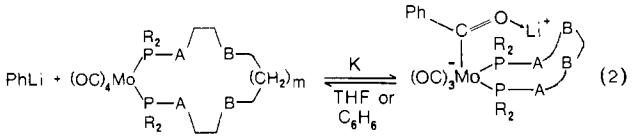
[a] Errors in individual K values vary from ±40% to ±15% depending on the magnitude of K (largest and smallest values have higher percent errors).

of the benzoylate complex **2** (M = Mo; R = Ph), as determined by X-ray crystallography, are shown in Figure 2. The benzoylate oxygen (O_1) and the diphosphinite "backbone" oxygens (O_2–O_5) adopt a conformation whereby five oxygen atoms define a cavity with a radius of ca. 2.0 Å (Li–O separation) in which the Li^+ cation resides. To a close approximation the benzoylate oxygen (O_1) and the two P–O oxygens (O_2 and O_3) occupy three of the four "tetrahedral sites" about Li^+, while the two ether oxygens (O_4 and O_5) are symmetrically placed about the fourth tetrahedral position. The "Mo(PhCOLi)" unit, which is approximately planar, has bond angles close to that expected for "sp^2" carbon and oxygen. The benzoylate CO bond (1.26 Å) is only slightly longer than a typical C=O double bond, while the Mo–C(O)Ph bond (2.25 Å) is ca. 0.1 Å shorter than expected for a Mo–C(sp^2) single bond.[15,16] This indicates that the majority of the negative charge is delocalized on the "$Mo(CO)_3$" moiety.

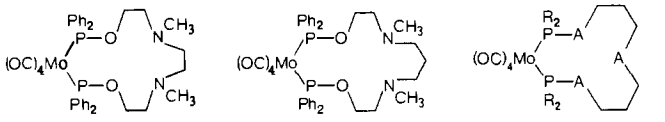
The additional driving force that makes reaction 1 thermodynamically favorable [relative to *cis*-$Mo(CO)_4(PR_3)_2$ complexes in general] is *preferential cation binding by the basic groups on*

(15) An Mo(O)–C(sp^2) single bond length is estimated to be ca. 2.33 Å by using the W–C bond length in $[(CO)_5WCHPh(OMe)]^-$[16] as being a reasonable estimate of a Mo(O)–C(sp^3) (2.34 Å).
(16) Casey, C. P.; Polichnowski, S. W.; Tuinstra, H. E.; Albin, L. D.; Calabrese, J. C. *Inorg. Chem.* **1978**, *17*, 3045.

the diphosphinite ligand together with the "benzoylate-acylate-type" oxygen in the product molecule. In order to assess the magnitude of this effect and factors which favor it we have prepared and fully characterized the series of complexes **3–6** (yields 5–50%) via procedures analogous to the preparation of **1**. Stable benzoylate and acylate complexes structurally analogous to **2** (see Figure 2) have been isolated from the reaction of RLi with **3**, **4**, and **5a, b**. Infrared spectroscopy (ν_{CO} region) may be used to study the solution equilibrium 2 for the series of complexes **1** and **3–6**



(2)



3 **4**

5a, R = Ph; A = O
b, R = Et; A = O
6a, R = Ph; A = NCH_3
b, R = Et; A = NCH_3

(e.g., see Figure 3). Selected equilibrium constants K (defined as $([Mo(CO)_3(RCOLi)P_2]/([Mo(CO)_4P_2][RLi]))$ are given in Table I together with ν_{CO} data for the $Mo(CO)_4P_2$ complexes. Values of K vary from $<10^{-2}$ L mol^{-1} for **6**/PhLi systems to $>10^5$ L mol^{-1} for the **3**/PhLi system. The data indicate that the benzoylate product in reaction 2 is favored by B = NMe > O and A = O ≫ NMe and the 2,2,2 ligand > 3,3 ligand > 2,3,2 ligand. Features which favor Li^+ binding in the product molecule are the following: (i) A ligand should be one donor atom short of providing Li^+ with a "full" coordination sphere [compound **1** (n = 4) complexes Li^+ but does not react to a significant extent with RLi). (ii) The ligand should be of a suitable size (12–14 atom ring). (iii) The ligand must accommodate the stereochemical requirements of the bridging M-C=O→Li^+ unit (molecular models indicate that steric interactions between PPh_2 and NMe groups for **6a** effectively prevent this complex from meeting this requirement). (iv) Atoms A and B should be as basic as possible. Thus B = NMe > O [e.g., compare **3** with **1** (n = 3)] and A = O ≫ NMe (e.g., compare **5b** with **6b**). [N→P π delocalization of the nitrogen lone pair effectively reduces the basicity of the P–N unit below that for P–O.[17] Delocalization of one of the P–O oxygen lone pairs onto phosphorus is also apparent in the molecular structure of **2** (M = Mo, R = Ph; Figure 2). The bond angles about the phosphinite oxygens are consistent with trigonal planar oxygen (e.g., ∠POC = 123, ∠POLi = 120, ∠LiOC = 117°)].

A comparison of the equilibrium data (Table I) for the reaction of **3** with PhLi vs. **6** with PhLi indicates that *preferential Li^+ binding in the product molecule can contribute ca. 9 kcal mol^{-1} of additional stabilization for the* **3** *system.* Thus cation binding by suitably designed ligands can provide *very significant* additional activation with respect to the reactions of coordinated carbon monoxide. Synthetic studies and investigations of metal carbonyls containing mono- and di-P-donor ligands with "pseudo-crown-ether" characteristics and capable of complexing Li^+, Mg^{2+}, and Al^{3+} are currently in progress.

Acknowledgment. Financial assistance from the Natural Sciences and Engineering Research Council of Canada is greatly appreciated.

Supplementary Material Available: A list of atomic coordinates and thermal parameters for $(OC)_3Mo(PhCOLi)[Ph_2P(OCH_2CH_2)_3OPPh_2]$, complex **2** (M = Mo, R = Ph) (5 pages). Ordering information is given on any current masthead page.

(17) Grec, D.; Hubert-Pfalzgrat, L. G.; Riess, J. G.; Grand, A. *J. Am. Chem. Soc.* **1980**, *102*, 7133 and references therein.

Autorecycling Oxidation of Alcohols Catalyzed by Pyridodipyrimidines as an NAD(P)$^+$ Model

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The alcohol dehydrogenases catalyzing the interconversion between carbonyl compounds and alcohols require NAD(P)$^+$/NAD(P)H as coenzymes. In the biomimetic reactions, both classes of the N-substituted 1,4-dihydronicotinamides and the Hantzsch esters have been widely used as models of NAD(P)H.[1] However, there are few examples for the NAD(P)$^+$ model oxidation of alcohol substrates,[2-5] because thermodynamically the redox equilibrium favors the formation of the pyridinium ion. Furthermore these model oxidations of alcohols proceeded only with the aid of very strong base[6] and gave the carbonyl compounds in stoichiometric yields.

Recently we reported that 5-deazaflavins[7] and their analogues such as 4-deazatoxoflavins[8] were considered to be NAD(P)$^+$ models which oxidized alcohols under weakly basic conditions and thereupon exhibited some recycling in the oxidation giving carbonyl compounds in more than 100% yield.

We here report an efficient and autorecycling oxidation of alcohols which is catalyzed by the new type NAD(P)$^+$ model working *under neutral conditions.* The NAD(P)$^+$ models used in the present study are two kinds of pyridodipyrimidines, 3,7,10-trisubstituted pyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8-(3*H*,10*H*,7*H*,9*H*)-tetrones (I) and 3,8,10-trisubstituted pyrido-[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones (II).

The pyridodipyrimidines (I and II) are structurally cyclized compounds of the amino analogues of the Hantzsch esters and also have a conjugated system similar to that of 5-deazaflavins. Furthermore, one of canonical forms can be considered as a model of the nicotinamide nucleotide protected by annelation ("masked NAD$^+$ analogue") (Scheme I). Thus it was expected that I and II abstract hydrogen (or its equivalents) from alcohol substrates. In fact, I and II have been found to oxidize a variety of alcohols under neutral conditions (in the absence of base) to yield the corresponding carbonyl compounds, and, furthermore, a remarkable autorecycling in the oxidation was observed.

Compounds I and II were synthesized by the condensation of the corresponding 6-chloro-5-formyluracils[9] with appropriate 6-(substituted-amino)uracils (for Ia–n) or with appropriate 6-(alkylamino)-2-phenylpyrimidine-4(3*H*)-ones[10] (for IIa–h) in

(1) (a) R. J. Kill and D. A. Widdowson, in "Bioorganic Chemistry", Vol. 4, E. E. van Tammelen, Ed., Academic Press, 1978, p 239; (b) T. J. van Bergen, D. M. Hedstrand, W. H. Kruizinga, and R. M. Kellog, *J. Org. Chem.*, 44, 4953 (1979); (c) A. Ohno, K. Ikeguchi, T. Kimura, and S. Oka, *J. Am. Chem. Soc.*, **101**, 7036 (1979); (d) R. A. Gase and U. K. Pandit, *ibid.*, **101**, 7059 (1979).

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(5) S. Shinkai, H. Hamada, H. Kuroda, and O. Manabe, *Chem. Lett.*, 1235 (1980).

(6) Exceptionally, Wallenfels and Hanstein[2] reported the oxidation of fluorenol to fluorenone by *N*-methyl-3,4,5-tricyanopyridinium perchlorate under neutral conditions. Although this unusual NAD(P)$^+$ model has very high electron affinity by virture of the three cyano groups, the yield of fluorenone was still only 8%.

(7) (a) F. Yoneda, Y. Sakuma, and P. Hemmerich, *J. Chem. Soc., Chem. Commn.*, 825 (1977); (b) F. Yoneda, K. Tsukuda, K. Shinozuka, F. Hirayama, K. Uekama, and A. Koshiro, *Chem. Pharm. Bull.*, **28**, 3049 (1980); (c) F. Yoneda, K. Mori, M. Ono, Y. Kadokawa, E. Nagao, and H. Yamaguchi, *ibid.*, **28**, 3576 (1980); (d) F. Yoneda, K. Mori, S. Matsuo, Y. Kadokawa, and Y. Sakuma, *J. Chem. Soc., Perkin Trans. 1*, 1836 (1981).

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(10) F. Yoneda and T. Nagamatsu, *J. Chem. Soc., Perkin Trans. 1*, 1547 (1976).

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