the ground state, we see for all three substituted molecules a general trend indicating alternation of charge sign on moving outward from the molecular center. On consideration of the atoms of the guanidinium moiety, the central carbons are highly positive, the nitrogens are highly negative, and the hydrogens are highly positive. The substituents have the effect of reducing the negative charge on the nitrogen to which they are attached, the magnitude of this effect decreasing in the order F, $NH_2$, $CH_3$.

One may also notice in passing that for the amino substitution the guanidinium hydrogen involved in hydrogen bonding is very positive, thus presumably enhancing its role as a hydrogen donor in hydrogen bond formation. Comparing the hydrogens of the amino and methyl substituents indicates the former to be much more positive.

## Summary and Conclusions

It appears that substitutions of the type modeled here do not much affect the planar "Y" framework of the guanidinium ion. They do, however, noticeably perturb the magnitude of single rotational barriers. The barrier changes, compared with the guanidinium case, are small for substitution by a methyl group, $\pm 2$ kcal mol$^{-1}$, but are larger for fluoro and amino substitution, $\pm 10$ kcal mol$^{-1}$. The range of barrier changes is not unreasonable judged against the NMR barriers that have been measured for guanidinium and substituted guanidinium. The charge analysis presented here does much to rationalize these barrier changes in terms of field effects, hydrogen bonds, and Y aromaticity.

The $sp^3$ hybrids of the methyl and amino substituents adopt similar orientations with respect to the molecular plane. Both substituents place a hydrogen symmetrically above and below the plane and, as one might think, enhance the width of the guanidinium molecule to the same extent. Importantly, however, the amino hydrogens are very positive, having a net charge of +0.382. Compare this charge to that of water (+0.394), computed by using the same basis as used here.[1] In so far as hydrogen bonds are largely electrostatic in character, these amino hydrogens will be good hydrogen donors in such bonds. The methyl hydrogens in contrast, however, are much less positive with net charges of +0.217 and +0.250 and cannot be expected to form hydrogen bonds. This contrast in hydrogen bonding is consistent with the relative effective width of the amino- and methyl-substituted guanidiniums in the sodium pore experiments mentioned earlier. The high net positive charge of the amino hydrogens is consistent with formation of strong hydrogen bonds in the sodium pore and a reduced effective width, allowing its passage through the pore. In fact, for the series X = H, $NH_2$, and $CH_3$, it is interesting that the measured permeability ratio[3] $P_X/P_{NA^+}$ decreases monotonically (0.13 to 0.06 to 0.01), in good correlation with the monotonic decrease in net atomic charge on substituent hydrogen (+0.435 to +0.382 to +0.218).

It is significant that substitution (at least that studied here) does not have a large effect on the positive charge of those hydrogens attached to unsubstituted nitrogens in the guanidinium moiety. The charges were seen to go from a minimum value of +0.425 to a maximum value of +0.469. Hence these hydrogens maintain their suitability for acting as hydrogen donors to hydrogen bonds. This fact is of utmost importance in the chemistry of substituted guanidinium ions. Applying this to tetradotoxin, we cannot expect that substitutions on the toxin will much effect its guanidinium fragment's tendency to form hydrogen bonds. Insofar as substitutions effect toxin activity, such effects would seem to lie with other mechanisms. Applying this to arginine, one sees its guanidinium fragment will suitably bond with carboxyl groups as required by the light-conversion mechanism mentioned earlier.

**Acknowledgment.** L.J.M. thanks Dr. Thomas Beattie of Merck Chemical Corp. and Tonis Oja for informative discussions on substituted guanidinium molecules. This work was done during tenure of a grant from the Research Foundation of the City University of New York.

**Registry No. 1a**, 43531-41-5; **1b**, 77060-44-7; **1c**, 77060-45-8; **1d**, 77060-46-9.

---

# Coenzyme Models. 28. Facile Oxidation of Alcohols and Amines by 3-Hydroxy-*N*-methylacridinium Ion, a New NAD$^+$ Model Compound[1]

Seiji Shinkai,* Hisatake Hamada, Hideo Kuroda, and Osamu Manabe

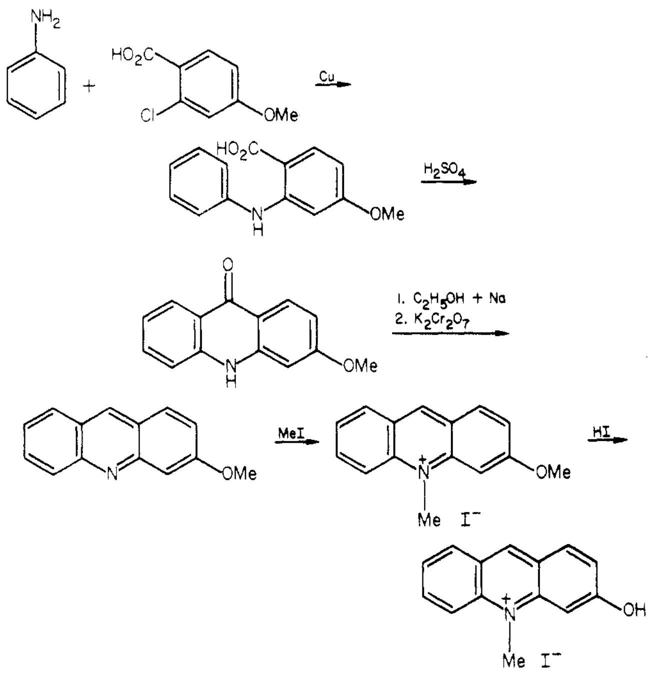
*Department of Industrial Chemistry, Faculty of Engineering, Nagasaki University, Nagasaki 852, Japan*

*Received December 16, 1980*

The title compound (Ac$^+$OH) was synthesized for the purpose of developing a new NAD$^+$ model compound which is capable of oxidizing alcohols and amines. The absorption spectrum of Ac$^+$OH was similar to that of *N*-methylacridinium ion (Ac$^+$) in the acidic pH region and to that of 5-deazaflavin in the basic pH region. The absorption spectrum of the reduced form was analogous to that of 3-aminophenol. The reduced form which was prepared by $NaBH_4$ reduction was promptly reoxidized by molecular oxygen. With the aid of potassium *tert*-butoxide, Ac$^+$OH oxidized benzyl alcohol and cyclohexanol to the corresponding aldehyde and ketone in almost quantitative yields. In contrast, Ac$^+$ was totally useless as an oxidant under the same reaction conditions. Benzylamine was oxidized by Ac$^+$ to benzaldehyde in low yields (11–24%). On the other hand, the oxidation by Ac$^+$OH occurred in good yields (82–88%). When the reaction was carried out under an oxygen stream, the yield calculated on the basis of Ac$^+$OH was enhanced up to 1800–2200%. The results indicate that Ac$^+$OH acts as an effective turnover oxidizing agent and that the 3-hydroxyl group plays a crucial role in the redox reactions occurring on the acridinium nucleus. This is the first example of the facile oxidation of alcohols and amines which mimics the catalytic behavior of NAD$^+$ coenzyme.

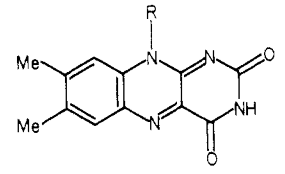
In alcohol dehydrogenases, the interconversion of aldehydes (ketones) and alcohols occurs in conjunction with that of NADH and NAD$^+$ coenzymes. Since Westheimer's pioneering studies,[2] considerable interest has centered

Scheme I

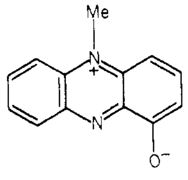


around the model investigation of NADH-dependent enzymes. In contrast to a number of investigations on the NADH model reduction of carbonyl substrates,[3-6] there are few examples for the NAD$^+$ model oxidation of alcohol substrates. Shirra and Suckling[7] have reported the oxidation of benzyl alkoxides by a pyridinium ion, but their conclusion has been to a large extent left ambiguous because it was derived only from the detection of benzaldehydes, and the reduced product (i.e., 1,4- or 1,2-dihydropyridine) was not identified. Wallenfels and Hanstein[8] showed that 9-fluorenol is oxidized to fluorenone (8% yield) by *N*-methyl-3,4,5-tricyanopyridinium ion which acts as a strong $\pi$ acid. More recently, Ohnishi and Kitami[9] carried out the oxidation of lithium alkoxides by pyridinium ions under strictly anaerobic conditions and detected the 1,4-dihydropyridines in 3.5–28% yields. Ohnishi[10] also showed that *N*-benzyl-3-carbamoylpyridinium perchlorate oxidizes a variety of aliphatic amines, giving the 1,4-dihydro compounds in 7–15% yields.

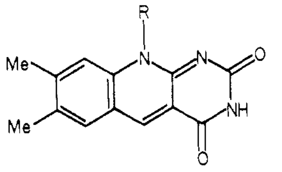
In the above-mentioned systems, the yields of the oxidized products are generally low. The fact indicates that the N-substituted pyridinium ions (conventional NAD$^+$ model compounds) have some defect as model compounds for the NAD$^+$ coenzyme. A clue to design a novel NAD$^+$ model compound was found in the recent publications of Yoneda and co-workers.[11,12] They demonstrated that 5-deazaflavin (or 5-deazaisoalloxazine) which is called "nicotinamide in flavin clothing"[13] is able to oxidize alcohols and amines in good yields. The results suggest that the NAD$^+$ model compound which involves within the molecular structure the characteristic of 5-deazaflavin would mimic the oxidation catalysis by NAD$^+$ coenzyme. Meanwhile, Sawyer et al.[14] demonstrated that the oxidation–reduction chemistry of pyocyanine has many similarities to that of flavin. It is thus expected that 3(or 5)-hydroxy-*N*-methylacridinium ion, which is regarded as a more precise NAD$^+$ model, would provide redox chemistry analogous to that of 5-deazaflavin. In this paper, we report that 3-hydroxy-*N*-methylacridinium iodide (Ac$^+$OH)



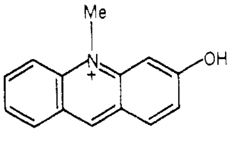
flavin



pyocyanine



5-deazaflavin



Ac$^+$OH

is able to oxidize alcohols and benzylamine in almost quantitative yields under the anaerobic conditions, whereas *N*-methylacridinium iodide (Ac$^+$) is almost useless as an oxidant. Furthermore, it is established that Ac$^+$OH is recycled ca. 20 times under aerobic conditions.

## Experimental Section

**Materials.** Ac$^+$OH was synthesized according to Scheme I. 5-Methoxydiphenylamine-2-carboxylic acid was prepared according to the method of Ullmann and Wagner[15] from aniline and 2-chloro-4-methoxybenzoic acid in the presence of copper powder: yield 40%; mp 174.5–176 °C (lit.[15] mp 178 °C).

Treatment of 5-methoxydiphenylamine-2-carboxylic acid in concentrated $H_2SO_4$ at 100 °C gave 3-methoxyacridone: 65% yield; mp 271–272 °C (lit.[16] mp 290 °C). This method is described in detail by Kliegl and Fehrle.[16] The melting point of this product was significantly different from that in the literature,[16] but the result of elemental analysis agreed well with that of the calculated value. Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.52; H, 4.84; N, 6.15.

3-Methoxyacridine was prepared according to the method of Borsche et al.[17] by the reduction of 3-methoxyacridone followed by the oxidation of formed 3-methoxyacridan: yield 36%; mp 90–91 °C (lit.[18] mp 88–90 °C).

3-Methoxyacridine (14 g, 0.067 mol) was treated at 45–50 °C with methyl iodide (38 g, 0.27 mol) in *N*,*N*-dimethylformamide.

---

(1) Preliminary communication: Shinkai, S.; Hamada, H.; Kuroda, H.; Manabe, O. *Chem. Lett.* **1980**, 1235.

(2) (a) Mauzerall, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2261. (b) Abeles, R. H.; Westheimer, F. H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1956**, *15*, 675. (c) Abeles, R. H.; Westheimer, F. H. *J. Am. Chem. Soc.* **1958**, *80*, 5459.

(3) Bruice, T. C.; Benkovic, S. In "Bioorganic Mechanisms"; W. A. Benjamin: New York, 1966; Vol. 2, Chapter 9.

(4) Kill, R. J.; Widdowson, D. A. In "Bioorganic Chemistry"; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 4, Chapter 8.

(5) Sigman, D. S.; Hajdu, J.; Creighton, D. J. In "Bioorganic Chemistry", van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 4, Chapter 14.

(6) (a) Shinkai, S. *Kagaku (Koyoto)* **1974**, *29*, 917. (b) Shinkai, S. *Ibid.* **1980**, *35*, 170.

(7) (a) Shirra, A.; Suckling, C. J. *Tetrahedron Lett.* **1975**, 3323. (b) *J. Chem. Soc., Perkin Trans. 2*, **1977**, 759.

(8) Wallenfels, K.; Hanstein, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 869.

(9) Ohnishi, Y.; Kitami, M. *Tetrahedron Lett.* **1978**, 4035.

(10) Ohnishi, Y. *Tetrahedron Lett.* **1977**, 2109.

(11) Yoneda, F.; Sakuma, Y.; Hemmerich, P. *J. Chem. Soc., Chem. Commun.* **1977**, 825.

(12) Yoneda, F.; Sakuma, Y.; Kadokawa, Y. *Chem. Lett.* **1979**, 1467.

(13) Walsh, C. *Acc. Chem. Res.* **1980**, *13*, 148.

(14) Morrison, M. M.; Seo, E. T.; Howie, J. K.; Sawyer, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 207.

(15) Ullmann, F.; Wagner, C. *Justus Liebigs Ann. Chem.* **1907**, *355*, 367.

(16) Kliegl, A.; Fehrle, A. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 1637.

(17) Borsche, W.; Runge, F.; Trautner, W. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1316.

(18) Sherwin, S. M.; Braz, C. I.; Yakubivich, A.; Varobeva, R. I.; Rabinovich, F. B. *J. Gen. Chem. USSR (Engl. Transl.)* **1938**, *8*, 884.

The precipitate (3-methoxy-*N*-methylacridinium iodide) was collected by suction and recrystallized from methyl alcohol: yield 74%; mp 237–238 °C dec; NMR ($Me_2SO$-$d_6$) $\delta$ 4.24 (3 H, s, *O*-$CH_3$), 4.72 (3 H, s, *N*-$CH_3$), 7.60–8.70 (7 H, m, aromatic protons), 9.89 (1 H, s, 9-H). Anal. Calcd for $C_{15}H_{14}NOI$: C, 51.30; H, 4.02; N, 3.99. Found: C, 50.78; H, 4.00; N, 4.04.

3-Hydroxy-*N*-methylacridinium iodide ($Ac^+OH$) was obtained by treatment of 3-methoxy-*N*-methylacridinium iodide with HI. 3-Methoxy-*N*-methylacridinium iodide (0.50 g, $1.4 \times 10^{-3}$ mol) was dissolved in 37% HI solution (30 g), and the mixture was heated at 120 °C for 8 h. When the mixture cooled, the precipitate was formed from the dark brown solution. The solution was decolorized with sodium thiosulfate, and the yellow precipitate was collected by suction. Recrystallization from *n*-butyl alcohol gave $Ac^+OH$: 53% yield; mp 260–261 °C dec; NMR ($Me_2SO$-$d_6$) $\delta$ 4.65 (3 H, s, *N*-$CH_3$), 5.35 (1 H, s, OH), 7.47–8.60 (7 H, m, aromatic protons), 9.76 (1 H, s, 9-H). Anal. Calcd for $C_{14}H_{12}NOI$: C, 49.87; H, 3.59; N, 4.15. Found: C, 49.74; H, 3.52; N, 4.09.

3-Hydroxy-*N*-methylacridan (AcHOH) was prepared by the $NaBH_4$ reduction of $Ac^+OH$. To 50 mL of a methanolic solution of $Ac^+OH$ (500 mg, $1.5 \times 10^{-3}$ mol) was added $NaBH_4$ (220 mg, $6.0 \times 10^{-3}$ mol) under a stream of $N_2$. The yellow color of $Ac^+OH$ disappeared within a few minutes. After 15 min, the reaction mixture was subjected to the HPLC analysis. A new peak which is probably ascribable to AcHOH was observed, but when the reaction mixture was left under aerobic conditions, this peak disappeared gradually, giving rise to a peak ascribable to $Ac^+OH$. After the solution was acidified to pH 1–2 with 1 N HCl, the methanolic solution was evaporated in vacuo. The oily residue was recovered, but the effort to isolate AcHOH in crystalline form ended in failure probably due to the contamination by $Ac^+OH$. We thus decided to show indirectly that the new peak observed immediately after the $NaBH_4$ reduction is ascribable to AcHOH.

$Ac^+OH$ (50 mg, $1.5 \times 10^{-4}$ mol) was dissolved in an anaerobic NMR capillary tube containing 1 mL of methanol-$d_4$. $NaBH_4$ (22 mg, $6.0 \times 10^{-4}$ mol) was added, and the NMR spectrum was recorded after 15 min: $\delta$ 3.32 (3 H, s, *N*-$CH_3$), 3.71 (2 H, s, 9-$CH_2$), 6.3–7.2 (7 H, m, aromatic protons). The spectrum was very similar to that of *N*-methylacridan in methanol-$d_4$ [$\delta$ 3.22 (3 H, s, *N*-$CH_3$), 3.79 (2 H, s, 9-$CH_2$), 6.8–7.2 (8 H, m, aromatic protons)], indicating that $Ac^+OH$ is reduced to AcHOH. To obtain the retention time of AcHOH, we immediately subjected the sample solution in the NMR capillary tube to the HPLC analysis. The UV–visible absorption spectrum was also recorded by diluting the sample solution.

**Oxidation of Alcohols.** The oxidation reactions were conducted in an ampule with a side arm. The typical procedure was as follows. A solution containing $Ac^+OH$ and substrate (alcohol) was placed in the bottom of the ampule, while potassium *tert*-butoxide was deposited in the side arm. The ampule was degassed carefully by thawing and freezing and sealed under reduced pressure. After equilibration of the ampule to the desired temperature, the content of the side arm was dissolved in the solution in the bottom. The reaction was stopped by adding a 4 N HCl solution immediately after breaking the ampule. In the oxidation of benzyl alcohol, the resultant solution was subjected to GLC analysis and the measurement of the UV–visible spectrum. In the oxidation of cyclohexanol, the solution was treated with 4-phenylsemicarbazide.

**Oxidation of Benzylamine.** The reaction was carried out by using a 50-mL, three-necked flask. After 10 h at 100 °C, the solution was poured into 100 mL of water, and the resultant solution was subjected to GLC analysis and the measurement of the UV–visible spectrum. In a separate experiment, we have confirmed by GLC that benzylidenebenzylamine ($C_6H_5CH{=}N$-$CH_2C_6H_5$) is quantitatively hydrolyzed to benzaldehyde and benzylamine by the above treatment.

**Miscellaneous Data.** UV–visible spectra were recorded at 30 °C on a Hitachi 200 spectrophotometer equipped with a thermostated cell holder. For the product analysis, high-pressure liquid chromatography (Shimadzu LC-3 instrument, Zorbax ODS column, water–methanol mixture) and gas chromatography (Shimadzu GC-4CM instrument, PEG 20M column, internal standard anisole) were used. The treatment with 4-phenylsemicarbazide and 2,4-dinitrophenylhydrazine was carried out according to the usual methods.[19]

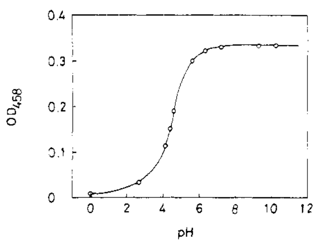


Figure 1. Phototitration of $Ac^+OH$ as a function of $OD_{458}$ at 30 °C and [$Ac^+OH$] = $2.00 \times 10^{-5}$ M.

## Results

**Absorption Spectra of $Ac^+OH$ and 3-Hydroxy-*N*-methylacridan (AcHOH).** The absorption spectrum of $Ac^+OH$ was dependent upon the medium pH. In 1 N HCl, $Ac^+OH$ gave rise to two absorption maxima at 417 nm ($\epsilon$ 8500) and 364 (45 800), the spectrum being similar to that of *N*-methylacridinium ion ($Ac^+$) in 1 N HCl ($\lambda_{max}$ 416 and 358 nm). With increasing medium pH, a new absorption maximum appeared in the visible region with a tight isosbestic point at 421 nm. The final spectrum at pH 11.24 [$\lambda_{max}$ 458 nm ($\epsilon$ 16 700), 362 (17 300), 347 (15 300)] is analogous to those of flavins and 5-deazaflavins (e.g., 3,10-dimethylisoalloxazine in ethanol, 438 and 334 nm; 3,10-dimethyl-5-deazaisoalloxazine in ethanol, 398 and 319.4 nm).[20,21] The OD value at 458 nm ($OD_{458}$) plotted as a function of pH resulted in a typical titration curve (Figure 1), the p$K_a$ value of the 3-hydroxyl group being estimated to be 4.63.

**$NaBH_4$ Reduction of $Ac^+OH$ and Reoxidation of AcHOH by Molecular Oxygen.** When $Ac^+OH$ in methanol was reduced by a fourfold excess $NaBH_4$ (see Experimental Section), the absorption band in the visible region disappeared completely, and a new absorption maximum appeared at 283 nm ($\epsilon$ 28 600). This spectrum is comparable with that of 3-aminophenol ($\lambda_{max}$ in methanol 287 nm).

Interestingly, we found that $AcHO^-$ in methanol is reoxidized by molecular oxygen. For example, when molecular oxygen was introduced into the methanol-$d_4$ solution of $AcHO^-$ prepared for the NMR measurement (see Experimental Section), the spectra of $Ac^+O^-$ (both NMR and UV–visible) were regenerated quantitatively within 3 h at room temperature. This result suggests that $Ac^+O^-$ would act as a ping-pong-type turnover oxidizing catalyst under aerobic conditions.

**Oxidation of Alcohols by $Ac^+OH$ and $Ac^+$.** The oxidation of benzyl alcohol and cyclohexanol by $Ac^+OH$ and $Ac^+$ in the presence of potassium *tert*-butoxide was carried out in an anaerobic ($N_2$), sealed ampule (Table I). After the benzyl alcohol solution containing $Ac^+OH$ had been mixed with potassium *tert*-butoxide in the side arm, the solution still had the color characteristic of $Ac^+O^-$ (yellow to orange). On the other hand, the reaction solution containing $Ac^+$ was decolorized immediately after being mixed with potassium *tert*-butoxide. The difference would reflect the apparent sensitivity of each oxidant toward the alkoxide nucleophile.

It is seen from Table I that with the aid of potassium *tert*-butoxide, $Ac^+O^-$ is capable of oxidizing alcohols in good yields (>81%). In contrast, these alcohols were

---

[19] Shriner, R. L.; Fuson, R. C.; Curtin, D. Y. In "The Systematic Identification of Organic Compounds"; Wiley: New York, 1956; p 218–219.

[20] Yoneda, F.; Sakuma, Y.; Ichiba, M.; Shinomura, K. *J. Am. Chem. Soc.* **1976**, *98*, 830.

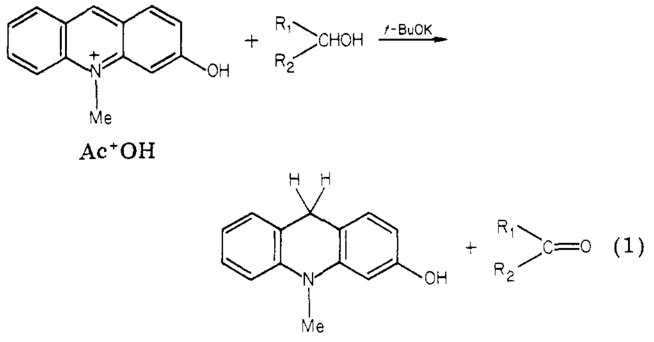
[21] Yoneda, F.; Sakuma, Y.; Mizumoto, S.; Ito, R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1805.

Table I. Oxidation of Alcohols by Ac$^+$OH[a]

| $R_1R_2CHOH$ (mL) | oxidant (mmol) | amt of $t$-BuOK, mmol | % yield of $R_1R_2$-C=O[b,d] |
|---|---|---|---|
| $C_6H_5CH_2OH$ (5) | none | 3.0 | trace |
| $C_6H_5CH_2OH$ (5) | Ac$^+$ (1.0) | 3.0 | trace |
| $C_6H_5CH_2OH$ (5) | Ac$^+$OH (1.0) | 4.0 | 81-84 |
| cyclohexanol (10)[c] | none | 3.0 | 0 |
| cyclohexanol (10)[c] | Ac$^+$ (1.0) | 3.0 | trace |
| cyclohexanol (10)[c] | Ac$^+$OH (1.0) | 4.0 | 94-99 |

[a] 80 °C, 8 h in the dark under anaerobic ($N_2$) conditions. [b] The yield of benzaldehyde was determined by the GLC method (internal standard was anisole). The yield of cyclohexanone was determined on the basis of the isolated cyclohexanone 4-phenylsemicarbazone. [c] *N,N*-Dimethylformamide (10 mL) was added to solubilize the oxidant. [d] "Yield" denotes benzaldehyde (or cyclohexanone)/Ac$^+$ (or Ac$^+$OH).

scarcely oxidized by Ac$^+$, indicating that Ac$^+$ is totally useless as an oxidizing agent. After the mixture was allowed to stand 8 h at 80 °C, an aliquot was withdrawn from the reaction mixture of Ac$^+$OH plus benzyl alcohol and diluted with an oxygen-saturated solution (pH 8.0). The absorption spectrum taken immediately after dilution was in accord with that of AcHO$^-$, and within a few hours the spectrum characteristic of Ac$^+$O$^-$ ($\lambda_{max}$ 458 nm) was regenerated. When the aliquot was immediately subjected to HPLC analysis (see Experimental Section), the retention time of the third peak, not including those of benzyl alcohol and benzaldehyde, was identical with that of AcHO$^-$ prepared by $NaBH_4$ reduction. These results consistently indicate that the oxidation of the alcohols occurs coupled to the reduction of Ac$^+$O$^-$ (eq 1).



Ac$^+$OH

AcHOH

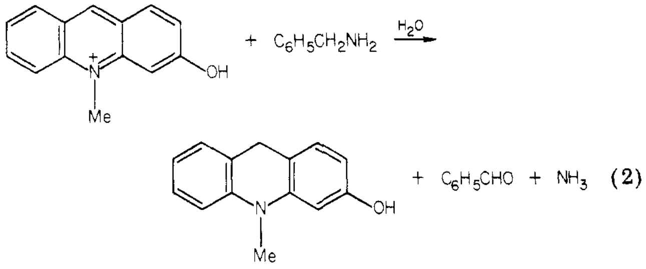
The oxidation of the alcohols under aerobic conditions was not performed, for the alcohols were significantly oxidized by molecular oxygen in the presence of potassium *tert*-butoxide. The ability of Ac$^+$O$^-$ as a turnover oxidizing catalyst was assessed with the following benzylamine substrate, since benzylamine was not oxidized by molecular oxygen under the experimental conditions.

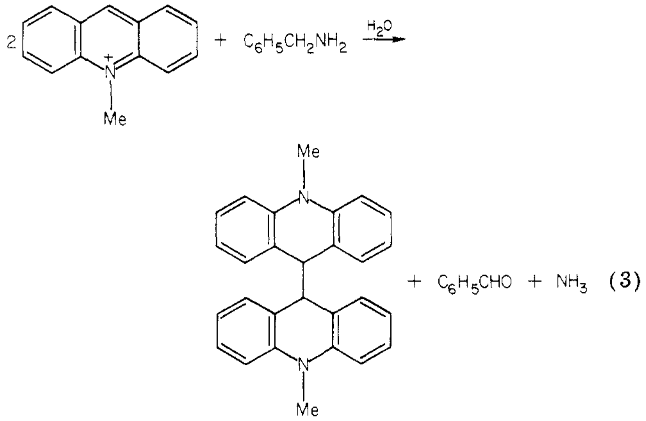
**Oxidation of Benzylamine by Ac$^+$OH and Ac$^+$ to Benzaldehyde.** The results are summarized in Table II. When the oxidation by Ac$^+$OH was carried out under anaerobic conditions, the final solution showed an absorption spectrum attributable to a mixture of AcHO$^-$ and Ac$^+$O$^-$. On the other hand, when the anaerobic solution oxidized by Ac$^+$ was poured into a ten times excess of water, a precipitate was recovered. This material was identified as 10,10′-dimethyl-9,9′-biacridan: mp 263–267 °C (lit.[22] mp 271 °C); mass spectrum, *m/e* 388 (M$^+$), fragment peak at 194. In the aqueous system (containing 5 mL of water), for instance, the amount of benzaldehyde produced (0.22 mmol) was almost equal to that of 10,10′-dimethyl-9,9′-biacridan (0.20 mmol). This allows one to conclude that the oxidation of 1 mol of benzylamine to benzaldehyde requires 2 mol of Ac$^+$. These findings are summarized by eq 2 and 3.

Table II. Oxidation of Benzylamine by Ac$^+$OH[a]

| amt of $H_2O$, mL | oxidant (mmol) | reaction atmosphere | % yield of benzaldehyde[b] |
|---|---|---|---|
| 5 | none | $O_2$ | 0 |
| 5 | Ac$^+$ (0.93) | $N_2$ | 17-24[c] |
| 5 | Ac$^+$ (0.93) | $O_2$ | 11-14 |
| 0 | Ac$^+$ (0.30) | $N_2$ | 37 |
| 0 | Ac$^+$ (0.30) | $O_2$ | 56 |
| 5 | Ac$^+$OH (0.89) | $N_2$ | 35[d] |
| 5 | Ac$^+$OH (0.89) | $O_2$ | 122-149[e] |
| 0 | Ac$^+$OH (0.10) | $N_2$ | 82-88 |
| 0 | Ac$^+$OH (0.10) | $O_2$ | 1800-2200 |

[a] 100 °C, 10 h in the dark. The amount of benzylamine was 5 mL in every case. [b] "Yield" denotes benzaldehyde/Ac$^+$ (or Ac$^+$OH). [c] The yield of 17-24% corresponds to 0.16-0.22 mmol of benzaldehyde. In the same run (24% yield), 0.20 mmol of 10,10′-dimethyl-9,9′-biacridan was isolated. [d] The yield determined by the 2,4-dinitrophenylhydrazone method was 34%. [e] The yield determined by the 2,4-dinitrophenylhydrazone method was 134%.





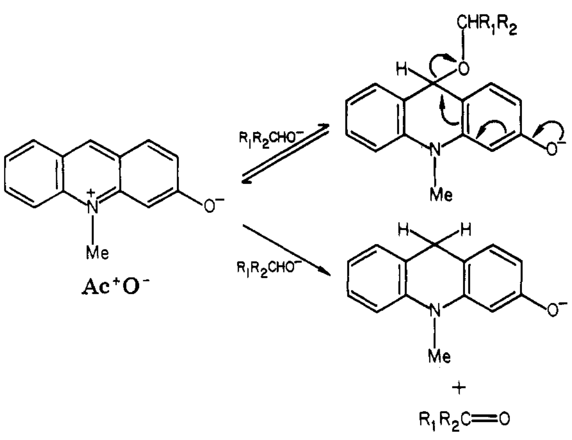
It is seen from Table II that in the aqueous sytem the yield of the Ac$^+$OH oxidation (35%) does not greatly exceed that of the Ac$^+$ oxidation (17–24%). Introduction of molecular oxygen into the Ac$^+$OH oxidation system markedly improved the yield (122–149%), whereas the aerobic yield of the Ac$^+$ oxidation (11–14%) was almost comparable with the anaerobic one. The result clearly indicates that only Ac$^+$OH acts as a turnover oxidizing catalyst.

The yield of the oxidation product was further enhanced in the nonaqueous system (no water added). The anaerobic yield was very high (82–88%), and the aerobic yield

---

[22] Moder, F.; Zanker, V. *Chem. Ber.* **1964**, *97*, 2418.

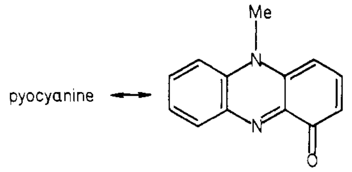
Scheme II



was enhanced up to 1800–2200%! The result implies that Ac$^+$O$^-$ is recycled ca. 20 times.

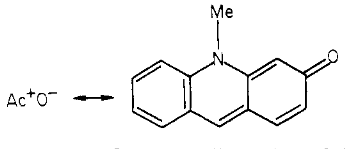
## Discussion

The fact that the oxidation–reduction chemistry of pyocyanine has similarities to that of flavin[14] would be associated with the contribution of the following resonance structure (eq 4).



(4)

The absorption spectrum of Ac$^+$OH in acidic aqueous solution is similar to that of Ac$^+$. The p$K_a$ value of the 3-hydroxyl group of Ac$^+$OH being 4.63, the reacting species under the experimental conditions is zwitterionic Ac$^+$O$^-$. This species would have the following resonance structure (eq 5)

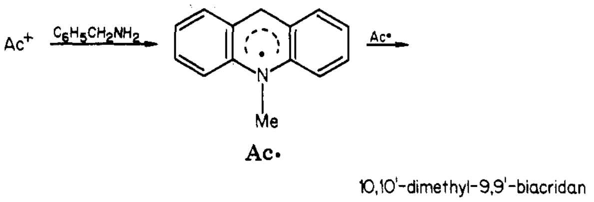


(5)

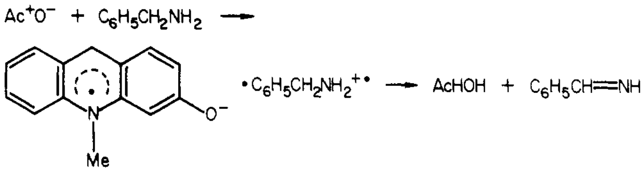
which is analogous to 5-deazaisoalloxazine. The absorption spectrum of the reduced form (AcHOH) is similar to that of 3-aminophenol. Hence, this new NAD$^+$ model compound would have the characteristics of Ac$^+$, 5-deazaisoalloxazine, and 3-aminophenol, depending on the medium pH and the redox state.

It is most interesting to consider why Ac$^+$O$^-$ is able to oxidize alcohols and Ac$^+$ is not. With the supposition that the Ac$^+$O$^-$ oxidation of alcohols takes place in the presence of alkoxide ion, two competitive reactions are conceivable (Scheme II): (i) fast, reversible adduct formation between Ac$^+$O$^-$ and alkoxide ion and (ii) slow, irreversible "hydride" (or its equivalent) transfer from alkoxide ion to Ac$^+$O$^-$. It has been noticed that the 9-position of Ac$^+$ is very reactive toward nucleophiles.[23] Hence, the immediate decolorization after the benzyl alcohol solution containing Ac$^+$ is mixed with potassium *tert*-butoxide indicates that Ac$^+$ in the reaction medium is rapidly converted to the adduct with benzyl alkoxide ion. This means that Ac$^+$ which may be effective as oxidant has been scavenged out in the presence of potassium *tert*-butoxide. The 4-position of 1-substituted nicotinamide salts is also reactive toward nucleophiles.[3-6] The low reactivity of 1-substituted nicotinamide salts (conventional NAD$^+$ model compounds) as oxidants[9] may be also attributed (at least partially) to adduct formation.[24] On the other hand, the solution color of Ac$^+$O$^-$ remained after mixing with potassium *tert*-butoxide. One may thus presume that the electron-donating nature of the 3-hydroxyl group makes the adduct with Ac$^+$O$^-$ more unstable than that with Ac$^+$. In other words, the concentration of Ac$^+$O$^-$ which is effective as oxidant is significantly high even in the presence of potassium *tert*-butoxide. The situation would allow slow, irreversible hydrogen transfer from alkoxide ion to Ac$^+$O$^-$.

Table II indicates that in the oxidation of benzylamine Ac$^+$ acts as a simple one-electron oxidant, whereas Ac$^+$OH acts as a two-electron-carrying shuttle. When 1-substituted nicotinamide salts are reduced by one-electron reducing agents (including electrochemical reduction), the main products are the dimers.[25-29] Hence, one may presume that the oxidation of benzylamine by Ac$^+$ occurs via a one-electron transfer mechanism involving the formation of a *N*-methylacridinium radical species (Ac·, eq 6).



(6)



(7)

Probably, the initial step of the Ac$^+$O$^-$ oxidation would also be a one-electron transfer (eq 7). The essential difference between two oxidants is that the intermediary radical species from Ac$^+$O$^-$ bears an anionic charge which would form the ion-paired complex with $C_6H_5CH_2NH_2^{+}\cdot$, whereas that from Ac$^+$ is neutral. The formation of the ion-radical pair probably suppresses the dimerization and facilitates further quasi-intramolecular transfer of e + H$^+$ or H·.

Although the Ac$^+$O$^-$ oxidation of benzylamine to benzylideneamine occurred in recycle even in the aqueous system, a remarkable amount of recycling was found in the nonaqueous system. A similar phenomenon was noticed by Yoneda et al. in the oxidation by 5-deazaisoalloxazine,[12] bent 5-deazaisoalloxazine,[30] and 4-deazatoxoflavin.[31] The origin of the remarkable solvent effect on the recycling number was not explained clearly by Yoneda et al.[12,30,31] The mechanistic investigation is now continued in this laboratory.

In conclusion, the present study demonstrates that Ac$^+$OH serves as an interesting oxidizing agent which imitates the catalytic behavior of NAD$^+$. Clearly, the 3-

---

[23] Hajdu, J.; Sigman, D. S. *J. Am. Chem. Soc.* **1975**, *97*, 3524.

[24] Ohnishi, Y., private communication.

[25] Santhanam, K. S. V.; Elving, P. J. *J. Am. Chem. Soc.* **1973**, *95*, 5482.

[26] Moriconi, E. J.; Misner, R. E. *J. Org. Chem.* **1969**, *34*, 3672.

[27] Weitz, E.; König, T.; von Wistinghausen, L. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 153.

[28] Wallenfels, K.; Gellrich, M. *Chem. Ber.* **1959**, *92*, 1406.

[29] Kano, K.; Matsuo, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3269.

[30] Yoneda, F.; Ono, M.; Kira, K.; Tanaka, H.; Sakuma, Y.; Koshiro, A. *Chem. Lett.* **1980**, 817.

[31] Yoneda, F.; Nakagawa, K. *J. Chem. Soc., Chem. Commun.* **1980**, 878.

hydroxyl group is crucial in modifying an *N*-methylacridinium nucleus as an NAD$^+$ model oxidant. The excellent yields and turnover nature suggest that Ac$^+$OH would provide further interesting redox chemistry.

**Acknowledgment.** The authors thank Professor J. B. Jones and Dr. Y. Ohnishi for helpful discussions.

**Registry No.** Benzenemethanol, 100-51-6; cyclohexanol, 108-93-0; benzaldehyde, 100-52-7; cyclohexanone, 108-94-1; benzylamine, 100-46-9; benzaldehyde 2,4-DNP, 1157-84-2; aniline, 62-53-3; 2-chloro-4-methoxybenzoic acid, 21971-21-1; 5-methoxydiphenylamine-2-carboxylic acid, 19218-83-8; 3-methoxyacridone, 61736-68-3; 3-methoxyacridine, 23043-46-1; 3-methoxy-*N*-methylacridinium iodide, 75874-18-9; benzylidenebenzylamine, 780-25-6; AcOH, 77081-04-0; AcHOH, 77081-05-1.

---

# Frontier Molecular Orbital Theory of Substituent Effects on Regioselectivities of Nucleophilic Additions and Cycloadditions to Benzoquinones and Naphthoquinones

Melvin D. Rozeboom, Inga-Mai Tegmo-Larsson, and K. N. Houk*[1]

*Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803*

*Received September 7, 1979*

Experimental data on nucleophilic additions and cycloadditions of unsymmetrical electron-rich dienes to substituted benzoquinones and naphthoquinones have been used to derive generalizations about the preferred site of nucleophilic attack on donor-substituted, acceptor-substituted, and conjugatively substituted species. SCF ab initio molecular orbital calculations have been carried out on examples of all of these species with the STO-3G basis set. Where known, the experimentally preferred site of attack by nucleophiles is that position having the largest LUMO coefficient, unless a donor group is attached to that position. In cases where experimental data are unavailable, predictions as to the most reactive position of the quinone toward nucleophiles are made. Frontier molecular orbital (FMO) theory parallels resonance theory arguments used to explain regioselectivity but provides predictions for relative rates of attack at all carbons of the quinones.

Diels–Alder reactions involving cycloadditions of dienes to quinones have been valuable in elegant syntheses of many natural products. Cycloadditions to *p*-benzoquinones have been the cornerstones of syntheses of steroids,[2] cortisone,[3] reserpine, yohimbine, estrone, and terramycin,[4] among others. Corey's achievement of the stereospecific total synthesis of gibberellic acid is a recent demonstration of the utility of a regioselective Diels–Alder cycloaddition involving a substituted benzoquinone.[5]

Recent interest in quinone cycloadditions has intensified due to the feverish activity directed at the synthesis of anthracycline antibiotics such as adriamycin and daunomycin, two molecules of this class which are effective in cancer chemotherapy.[6–15] Synthetic approaches to these and related anthraquinones have been developed on the basis of Diels–Alder cycloadditions to naphthoquinones or anthraquinones,[6–16] and as a fringe benefit, much information has been accumulated about the regioselectivities of these cycloadditions. A resonance theory model has been developed to rationalize these results.[7] We have also recently elucidated the regioselectivity of cycloadditions to the substituted double bond of methoxybenzoquinones and methoxynaphthoquinones.[17] We report here a systematic investigation of the influence of substituents upon the shapes of the frontier molecular orbitals of benzoquinones and naphthoquinones. Because the majority of cycloadditions and additions to quinones involve electron-rich species (nucleophiles), we concentrate attention on substituent effects on the low-lying vacant molecular orbitals of the quinones. The lowest unoccupied molecular orbitals (LUMOs) of the quinones can be used in the context of frontier molecular orbital (FMO) theory to explain the orientation of nucleophilic additions and cycloadditions to unsymmetrical benzoquinones and naphthoquinones.[18] Predictions have also been made for

---

[1] Present address: Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

[2] Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1951**, *73*, 2403, 3546, 3548; **1952**, *74*, 4223.

[3] Sarett, L. H.; Arth, G. E.; Lukes, R. M.; Beyler, B. M.; Poos, G. I.; Johns, W. F.; Constantin, J. M. *J. Am. Chem. Soc.* **1952**, *74*, 4974.

[4] For a summary of these and others, see: Anand, N.; Bindra, J. S.; Ranganathan, S. "Art in Organic Synthesis"; Holden-Day: San Francisco, 1970.

[5] Corey, E. J.; Danheiser, R. L.; Chandrasekan, S.; Siret, P.; Keck, G. E.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8031. Corey, E. J.; Danheiser, R. L.; Chandrasekan, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 8034.

[6] Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr.; Lyding, J. M. *J. Am. Chem. Soc.* **1977**, *99*, 5513.

[7] (a) Kelly, T. R.; Goerner, R. N., Jr.; Gillard, J. W.; Prazak, B. K. *Tetrahedron Lett.* **1976**, 3869. (b) Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr. *Ibid.* **1976**, 3873. (c) Kelly, T. R. *Ibid.* **1978**, 1387. (d) Kelly, T. R.; Montury, M. *Ibid.* **1978**, 4309. (e) Kelly, T. R.; Montury, J. *Ibid.* *1978*, *4311*.

[8] Farina, F.; Prados, P. *Tetrahedron Lett.* **1979**, 477 and references therein.

[9] Boeckman, R. K., Jr.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098.

[10] Grandmaison, J.-L.; Brassard, P. *J. Org. Chem.* **1978**, *43*, 1435.

[11] Lee, E. W.; Martinez, A. P.; Smith, T. H.; Henry, D. W. *J. Org. Chem.* **1976**, *41*, 2296.

[12] Wiseman, J. R.; French, N. I.; Hallmark, R. K.; Chiong, K. G. *Tetrahedron Lett.* **1978**, 3765.

[13] (a) Kende, A. S.; Tsay, T.-G.; Mills, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 1967. (b) Kende, A. S.; Curran, D. P.; Tsay, T.-G.; Mills, J. E. *Tetrahedron Lett.* **1977**, 3537.

[14] Jung, M. E.; Lowe, J. A. *J. Org. Chem.* **1977**, *42*, 2371.

[15] Krohn, K.; Tolkiehn, K. *Tetrahedron Lett.* **1978**, 4023.

[16] Garland, R. B.; Palmer, J. A.; Schulz, J. A.; Sollman, P. B.; Pappo, R. *Tetrahedron Lett.* **1978**, 3669.

[17] Tegmo-Larsson, I.-M.; Rozeboom, M. D.; Rondan, N. G.; Houk, K. N. *Tetrahedron Lett.*, in press.

0022-3263/81/1946-2338$01.25/0 © 1981 American Chemical Society