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FACILE OXIDATION OF ALCOHOLS BY 3-HYDROXY-N-METHYLACRIDINIUM ION (A NEW NAD$^+$ MODEL COMPOUND)

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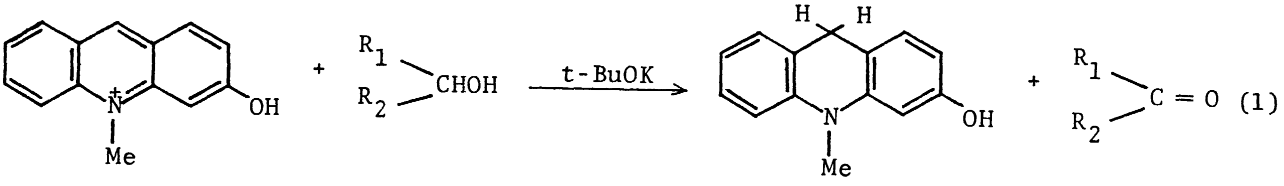
3-Hydroxy-N-methylacridinium iodide (Ac$^+$OH) oxidized alcohols with the aid of potassium t-butoxide, whereas N-methylacridinium iodide (Ac$^+$) could not oxidize alcohols under the same reaction conditions. The results indicate that the 3-hydroxyl group is crucial in modifying an N-methylacridinium nucleus as an NAD$^+$ model oxidizing agent.

In alcohol dehydrogenases, the interconversion of aldehydes (ketones) and alcohols occurs in couple to that of NADH and NAD$^+$ coenzymes. In contrast to a number of investigations on the NADH model reduction of carbonyl substrates,[1)] there are few examples for the NAD$^+$ model oxidation of alcohol substrates.[2-4)] Shirra and Suckling[3)] have reported the oxidation of benzyl alkoxides by a pyridinium ion, but their conclusion has been left ambiguous,[4,5)] because their discussions are based only on the detection of benzaldehydes and the reduced product (i.e., 1,4- or 1,2-dihydropyridine) was not identified. More recently, Ohnishi and Kitami[4)] carried out the oxidation of lithium alkoxides by pyridinium ions under strictly anaerobic conditions. They detected the 1,4-dihydropyridines in 3.5-28% yields. We here report a new NAD$^+$ model compound, 3-hydroxy-N-methylacridinium iodide (Ac$^+$OH) which oxidizes alcohols in high yields.



(1)

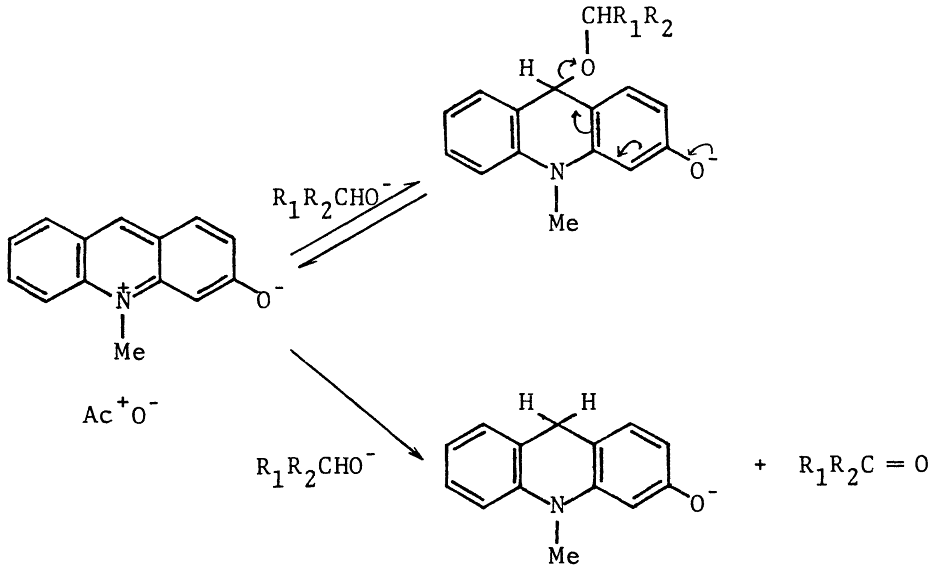
Ac$^+$OH   AcHOH

Ac$^+$OH (mp (dec) 260-261°C) was synthesized from 2-chloro-4-methoxybenzoic acid and aniline via five steps[6)] and was identified by its elemental analysis and IR and NMR spectrum. The absorption spectrum of Ac$^+$OH in aqueous solution was pH-dependent: λ_{max} 417 nm (ε 8500) in 1 N HCl, and λ_{max} 458 nm (ε 16700), 362 nm (ε 17300), and 347 nm (ε 15300) at pH 11.2. Based on the photo-titration at 30°C, we estimated the pK_a of 3-OH to be 4.63. Therefore, the reacting species under the following basic conditions is zwitterionic Ac$^+$O$^-$.

The typical oxidation procedure is as follows. Ac$^+$OH and alcohol were mixed in the bottom of an ampule, while potassium t-butoxide was deposited in the side arm of the ampule. The ampule was degassed carefully by thawing and freezing and sealed under reduced pressure. After equilibration of the ampule to 80°C, the content of the side arm was mixed with the solution in the bottom. The reaction was stopped by adjusting the solution pH to 1-2. The aliquot was withdrawn and was subjected to the spectral analysis, while the remaining solution was diluted with water, extracted by ether, and subjected to the GLC analysis and/or to the treatment with 4-phenylsemicarbazide. The results are summarized in Table 1. It is seen from Table 1 that Ac^+OH acts as an excellent oxidizing agent of benzyl alcohol and cyclohexanol in the presence of potassium t-butoxide, whereas N-methylacridinium iodide (Ac^+) gives only a trace amount of the carbonyl products.

The authentic sample of AcHOH was prepared from $NaBH_4$ and Ac^+OH in absolute methanol-d_4. In an anaerobic capillary tube, it showed the spectrum characteristic of $AcHO^-$.7) The absorption spectrum taken in an anaerobic Thunberg cuvette showed no absorption maximum from 300 to 600 nm. The sample withdrawn immediately after the oxidation reaction (Ac^+OH + benzyl alcohol + t-BuOK) also gave the spectrum identical to that of the $NaBH_4$ reduction. We found, however, that $AcHO^-$ is reoxidized by oxygen, the rate being accelerated in the presence of Ac^+OH. For example, the methanol-d_4 solution of $AcHO^-$ regenerated Ac^+O^- quantitatively within 3 h. We attempted to isolate AcHOH, but the recovered oily residue was identified in most part to be Ac^+OH. We finally abandoned to isolate AcHOH. Since the spectrum of Ac^+O^- is quantitatively regenerated from the reaction solution, we concluded that the oxidation of alcohols occurs in conjugation with the reduction of Ac^+O^-.

It is interesting to consider why Ac^+O^- is able to oxidize alcohols and Ac^+ is not. Supposing that Ac^+O^- oxidation of alcohols takes place in the presence of alkoxide ion, two competitive reactions are conceivable: (i) reversible adduct formation between Ac^+O^- and alkoxide (Eq. 2)8) and (ii) irreversible "hydride" (or its equivalent) transfer from alkoxide to NAD^+ (Eq. 3).



(2)

(3)

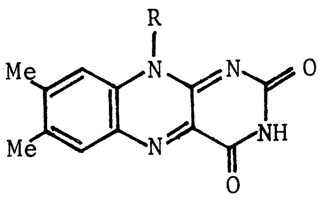
Table 1. Oxidation of alcohols by 3-hydroxy-N-methylacridinium iodide (Ac^+OH)[a]

Alcohol (ml) R_1R_2CHOH	Oxidant (mmole)	t-BuOK mmole	Yield(%) of $R_1R_2C=O$[b]
$C_6H_5CH_2OH$ (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

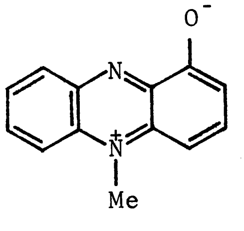
[a] 80°C, 8 h in the dark. [b] The yield of benzaldehyde was determined by the GLC method (internal standard: anisole). The yield of cyclohexanone was determined by the treatment with 4-phenylsemicarbazide. [c] 10 ml of DMF were added to solubilize the oxidant.

One may reasonably assume that the adduct with Ac^+O^- is more destabilized than that with Ac^+ owing to the electron-donating nature of 3-hydroxide group. It is suggested, therefore, that the 9-position of Ac^+O^- is "kinetically" insensitive to nucleophiles. Hence, the Ac^+O^- concentration effective as an oxidant is significantly enhanced even in the presence of alkoxide. In other words, a significant fraction of Ac^+ exists as the alkoxide adduct which is ineffective as an oxidant. In fact, the solution color of Ac^+ had disappeared immediately after mixing the reactants owing probably to adduct formation, whereas that of Ac^+O^- remained unfaded and disappeared rather gradually

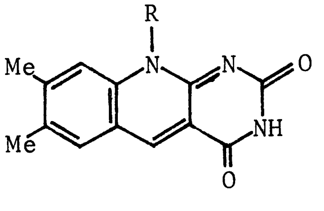
Recently, Sawyer et al.[9] reported that the oxidation-reduction chemistry of pyocyanine has many similarities to that of flavin.



Flavin



Pyocyanine



5-Deazaflavin

One may thus expect that Ac^+O^- has the electrochemical similarities to 5-deazaflavin. In fact, the absorption spectrum of Ac^+O^- is very similar to that of 5-deazaflavin. In this connection, it is very interesting to note that 5-deazaflavin is able to oxidize alcohols with the aid of base.[10] Further studies are currently under way in this laboratry.

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References and Notes

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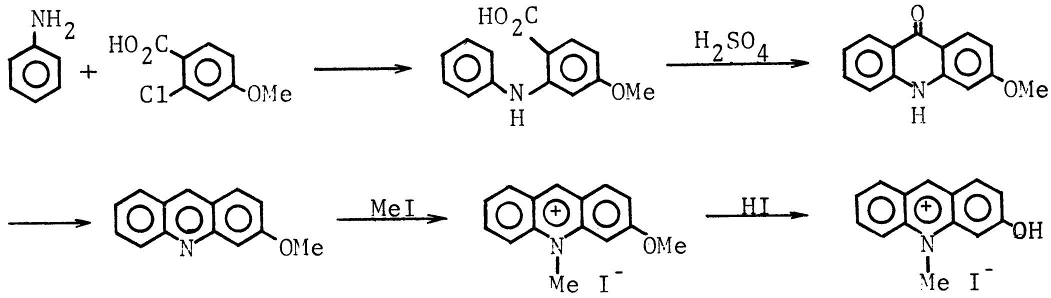

7) NMR (CD_3OD) of AcHOH: 3.32 ppm, 3H, N-CH_3; 3.71 ppm, 2H, 9-CH_2; 6.3-7.2 ppm, 7H, aromatic H.
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