Collman et al.[19] have recently reported the use of $NaHFe_2(CO)_8$ as a stoichiometric reagent for this reduction and have summarized various other methods. For substrates not containing a substituent $\beta$ to the carbonyl group, the easily carried out reaction conditions reported here are certainly of potential utility. With carvone (entry 8, Table IV), for example, the reaction rate on a similar scale reaction is quite comparable to the $NaHFe_2(CO)_8$ system for the first equivalent of substrate, and the system is still active for more substrate because the reactions are catalytic. Also, the system is not as sensitive to air, and substrates are taken directly from reagent bottles. The nearly total inhibition with $\beta$ substitution could actually be used in certain complex sytems to gain selectivity. Note that this catalyst does not generally react with other functional groups with the exception of halide substitution.[9d]

It is unlikely that phase-transfer catalysis is actually taking place in these reactions with ketones because the initial rate of the reactions is *not* accelerated by the phase-transfer reagent as was observed with the diene substrates. Presumably these ketone substrates can solubilize in the water phase sufficiently to allow reaction. The phase-transfer reagent does, however, substantially prevent catalyst decomposition, thus significantly increasing the amount of substrate that can be hydrogenated.

These reaction conditions did not prove to be useful with $\alpha,\beta$-unsaturated aldehydes. Low yields were obtained, and a substantial amount of polymeric materials formed in the reactions.

(19) Collman, J. P.; Finke, R. G.; Matlock, P. L.; Wahren, R.; Komoto, R. G.; Brauman, J. I. *J. Am. Chem. Soc.* **1978**, *100*, 1119–1140.

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**Registry No.** 2-methyl-1,3-butadiene, 78-79-5; 2-methyl-1-butene, 563-46-2; 2-methyl-2-butene, 513-35-9; 2,3-dimethyl-1,3-butadiene, 513-81-5; 2,3-dimethyl-1-butene, 563-78-0; 2,3-dimethyl-2-butene, 563-79-1; 1,3-pentadiene, 504-60-9; (*E*)-2-pentene, 646-04-8; (*Z*)-2-pentene, 627-20-3; (*E*)-1,1-dideuterio-1,3-pentadiene, 68167-88-4; (*E*)-1,1-dideuterio-2-pentene, 74366-55-5; (*E*)-5,5-dideuterio-2-pentene, 74366-566-6; (*E*)-2-methyl-1,3-pentadiene, 926-54-5; 4-methyl-1,3-pentadiene, 926-56-7; (*E*)-4-methyl-2-pentene, 674-76-0; 2-methyl-2-pentene, 625-27-4; 2,4-dimethyl-1,3-pentadiene, 1000-86-8; 2,4-dimethyl-1-pentene, 2213-32-3; 2,4-dimethyl-2-pentene, 625-65-0; (*E,Z*)-2,4-hexadiene, 5194-50-3; (*E,E*)-2,4-hexadiene, 5194-51-4; 3-hexene, 592-47-2; 2-hexene, 592-43-8; 1,3-cyclohexadiene, 592-57-4; cyclohexene, 110-83-8; 1,3,5-cycloheptatriene, 544-25-2; 1,3-cycloheptadiene, 4054-38-0; 1,4-cycloheptadiene, 7161-35-5; cycloheptene, 628-92-2; 3-buten-2-one, 78-94-4; 2-butanone, 78-93-3; 3-methyl-3-buten-2-one, 814-78-8; 3-methyl-2-butanone, 563-80-4; (*E*)-4-phenyl-3-buten-2-one, 1896-62-4; 4-phenyl-2-butanone, 2550-26-7; 2-cyclohexen-1-one, 930-68-7; cyclohexanone, 108-94-1; carvone, 99-49-0; *cis*-2-methyl-5-(1-methylethenyl)cyclohexanone, 3792-53-8; *trans*-2-methyl-5-(1-methylethenyl)cyclohexanone, 5948-04-9; (*R*)-pulegone, 89-82-7; (2*R*-*cis*)-5-methyl-2-(1-methylethyl)cyclohexanone, 1196-31-2; (2*S*-*trans*)-5-methyl-2-(1-methylethyl)cyclohexanone, 14073-97-3; $\beta$-ionone, 14901-07-6; (*E*)-4-(2,2,6-trimethylcyclohexylidene)-2-butanone, 65790-21-8; (*Z*)-4-(2,2,6-trimethylcyclohexylidene)-2-butanone, 65790-22-9; 2-cyclopenten-1-one, 930-30-0; cyclopentanone, 120-92-3; 2-methyl-2-cyclopenten-1-one, 1120-73-6; 2-methylcyclopentanone, 1120-72-5; 3-methyl-2-cyclopenten-1-one, 2758-18-1; 3-methylcyclopentanone, 1757-42-2; *p*-benzoquinone, 106-51-4; hydroquinone, 123-31-9; acrolein, 107-02-8; propionaldehyde, 123-38-6; methacrylaldehyde, 78-85-3; isobutyraldehyde, 78-84-2; (*E*)-crotonaldehyde, 123-73-9; butyraldehyde, 123-72-8; (*E*)-cinnamaldehyde, 14371-10-9; hydrocinnamaldehyde, 104-53-0; $(CH_3)_4NCl$, 75-57-0; $Et_3PhCH_2NCl$, 56-37-1; $Et_4NOH$, 77-98-5; $K_3[Co(CN)_5H]$, 18117-30-1; cycloheptene, 628-92-2.

# Methylation of Nucleosides with Trimethylsulfonium Hydroxide. Effects of Transition Metal Ions

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The effect of transition metal acetylacetonates [$M(AA)_n$] on the methylation of ribo- and deoxyribonucleosides with trimethylsulfonium hydroxide was studied. With ribonucleosides the metal complexes promoted O'-methylation at the 2' and 3' positions of the ribosyl group. A comparable effect was not observed in methylation of deoxyribonucleosides. These results are attributed to an increase in the nucleophilicity of the 2'-OH and 3'-OH groups of the ribosides through complex formation with the metal ion; such a complex cannot form with the deoxyribose derivatives. The activity of the metal ions studied for promoting this O'-methylation increased in the order $Mn^{2+} < Co^{2+} = Zn^{2+} < Ni^{2+} < Cu^{2+} < Fe^{3+}$. These $M(AA)_n$ also suppressed N-methylation of the purine and pyrimidine rings of adenosine and cytidine. It is suggested that this result may be caused by coordination of the metal ions with ring nitrogens.

## Introduction

An organic molecule complexed with a metal ion often exhibits reactivity considerably different from that of the uncomplexed molecule. When the molecule bears several reactive sites, the use of the metal ion may promote or suppress reactions at the complexed sites, leading to a selective synthetic method. This rationale stimulated us to examine effects of metal ions on an alkylation reaction of nucleosides. Treatment of ribonucleosides with diazomethane in the presence of Lewis acids such as $SnCl_4$ has been shown to produce the corresponding 2'-*O*-methyl and 3'-*O*-methyl derivatives in good yields.[1-3] A bidendate complex involving ribose 2'-OH and 3'-OH has been postulated as the role of the catalysts. However, many other metal salts containing $Cu^{2+}$, $Zn^{2+}$, etc. were not active in spite of their capabilities of forming similar complexes with

(1) M. J. Robins, S. R. Naik, and A. S. K. Lee, *J. Org. Chem.*, **39**, 1891 (1974).
(2) M. J. Robins, A. S. K. Lee, and F. A. Norris, *Carbohydrate Res.*, **41**, 304 (1975).
(3) M. J. Robins and S. R. Naik, *Biochim. Biophys. Acta*, **246**, 341 (1971).

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Table I. Product Yields (%) in Methylation of Ado by $Me_3SOH$ in the Presence of Various Metal Acetylacetonates [$M(AA)_n$][a]

| product | $M^{2+}$ none | $Mn^{2+}$ [b] | $Co^{2+}$ | $Zn^{2+}$ [b] | $Ni^{2+}$ | $Cu^{2+}$ | $Fe^{3+}$ |
|---|---|---|---|---|---|---|---|
| 2'-MeAdo | 18 | 28 | 27 | 40 | 28 | 41 | 40 |
| 3'-MeAdo | 7 | | 13 | 13 | 15 | 37 | 36 |
| 1-MeAdo | 4 | 12 | 8 | tr | 6 | tr | tr |
| $N^6$-MeAdo | 18 | | | 5 | 3 | tr | tr |
| $N^6$,2'-$Me_2$Ado | 11 | 7 | 8 | 6 | 15 | 5 | tr |
| $N^6$,3'-$Me_2$Ado | 4 | | 3 | 2 | 7 | 4 | tr |
| 2',3'-$Me_2$Ado | 5 | 6 | 6 | tr | 8 | 3 | tr |

[a] Reaction conditions: Ado-$Me_3SOH$-$M(AA)_n$-DMF = 1.0 mmoL/2.0 mmoL/0.5 mmoL/4.0 mL; temperature, 70 °C; time, 1 h. Tr refers to a trace yield. [b] Reaction mixture was not homogeneous.

ribonucleosides.[4,5] The reaction of 2',3'-*O*-(dibutylstannylene)uridine with methyl iodide has also been shown to provide a mixture of 2'-*O*-methyl- and 3'-*O*-methyluridines in good yields.[6] This methodology, however, could not be applied to methylation of other ribonucleosides.

We describe the effects of metal ions on the methylation of ribonucleosides, deoxyribonucleosides, and 2'-*O*-methylribonucleosides using trimethylsulfonium hydroxide ($Me_3SOH$) as a methylating agent.[7] It was found that metal ions increase methylation on ribose moieties at the expense of methylation on nitrogen heterocyclic moieties.

## Results and Discussion[8]

Methylation reactions were carried out by treating a mixture of a nucleoside, $Me_3SOH$, and a metal acetylacetonate [$M(AA)_n$] (mole ratio 1:2:1) in dimethylformamide (DMF) at 70 °C for 1 h in an atmosphere of nitrogen. $M(AA)_n$ was chosen as the source of the metal ion because of good solubility in DMF. Its ligand (AA) was methylated to give 3-methylacetylacetone to only a small extent [ca. 3–7% based on the amount of $M(AA)_n$ used]. As a methylating agent $Me_3SOH$ was used because its products, water and dimethyl sulfide, are too weak as ligands to interfere in methylation reactions.

Table I shows the results of methylation of Ado. $N^6$-MeAdo may have been formed by the Dimroth rearrangement[9] of 1-MeAdo. Although we have no experimental basis for this hypothesis, the N-1 position of Ado is much more nucleophilic than the 6-$NH_2$ group, and only 5% of aniline was converted into the *N*-methyl derivative under the conditions used. Similarly, $N^6$,2'-$Me_2$Ado and $N^6$,3'-$Me_2$Ado may be derived mainly from 1,2'-$Me_2$Ado and 1,3'-$Me_2$Ado, respectively.

Among various $M(AA)_n$ examined, $Cu(AA)_2$ and $Fe(AA)_3$ were especially effective in increasing the yields of 2'-MeAdo and 3'-MeAdo; the yields of N-methylated products decreased significantly. For instance, the extent of O'-methylation, which is represented by the sum of yields of 2'-O- and 3'-O-methylated adenosines, was increased to 76–90% from 45% in the absence of the metal complexes; the extent of N-methylation, which is represented by the sum of yields of $N^1$- and $N^6$-methylated adenosines, was suppressed to trace to 9% from 37% observed in the absence of the metal complexes. $Zn(AA)_2$ favored the formation of 2'-MeAdo over 3'-MeAdo.

Table II. Effects of $Cu(AA)_2$ on Methylation of Ado[a]

| mole ratio Ado:$Cu(AA)_2$ | N-methylation,[b] % | O'-methylation,[c] % | ratio of methylation at 2'-O:3'-O |
|---|---|---|---|
| 1:0 | 39 | 43 | 2.8:1 |
| 1:0.16 | 25 | 81 | 1.4:1 |
| 1:0.50 | 9 | 87 | 1.1:1 |
| 1:0.70 | 7 | 88 | 1.1:1 |
| 1:1.00 | 7 | 90 | 1.1:1 |

[a] Reaction conditions: Ado-$Me_3SOH$-DMF = 1.0 mmoL/2.0 mmoL/4 mL; temperature, 70 °C; time, 1 h. [b] The sum of yields of 1-MeAdo, $N^6$-MeAdo, $N^6$,2'-$Me_2$-Ado, and $N^6$,3'-$Me_2$Ado. [c] The sum yields of 2'-MeAdo, 3'-MeAdo, $N^6$,2'-$Me_2$Ado, $N^6$,3'-$Me_2$Ado, and 2',3'-$Me_2$-Ado.

Table III. Effects of $Fe(AA)_3$ on Methylation of Ado[a]

| mole ratio Ado:$Fe(AA)_3$ | N-methylation,[b] % | O'-methylation,[c] % | ratio of methylation at 2'-O:3'-O |
|---|---|---|---|
| 1:0.05 | 38 | 57 | 1.9:1 |
| 1:0.10 | 33 | 73 | 1.5:1 |
| 1:0.20 | 18 | 85 | 1.3:1 |
| 1:0.50 | tr | 76 | 1.1:1 |
| 1:0.75 | tr | 65 | 1.0:1 |

[a–c] See footnotes *a–c* of Table II, respectively.

Although the results with $Mn^{2+}$ and $Zn^{2+}$ complexes may have been affected by the fact that the reaction mixtures were not fully homogeneous, the order of increasing activity of the divalent metal ions in promoting O'-methylation was $Mn^{2+} < Co^{2+} = Zn^{2+} < Ni^{2+} < Cu^{2+}$; the order of increasing activity for suppressing N-methylation was $Ni^{2+} < Mn^{2+} = Co^{2+} < Zn^{2+} < Cu^{2+}$.[10]

The order for promoting O'-methylation is essentially the same as that given by Irving and Williams for the relative stabilities of divalent transition metal ion complexes.[11]

Of the trivalent metal ions investigated, $Fe^{3+}$ was the most active. $Mn^{3+}$ was effective only for suppressing N-methylation and did not affect O'-methylation, while $Cr^{3+}$ did not affect either O'-methylation or N-methylation.

(4) R. M. Izatt, J. J. Christensen, and J. H. Rytting, *Chem. Rev.*, 71, 439 (1971); G. L. Eichhorn, "Inorganic Biochemistry", Vol. 2, Elsevier Scientific Publishing Co., Amsterdam, 1973, p 1191.

(5) Y. H. Chao and D. R. Kearns, *J. Am. Chem. Soc.*, 99, 6425 (1977); H. Reinert and R. Weiss, *Hoppe-Seyler's Z. Physiol. Chem.*, 350, 1321 (1969).

(6) D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, 39, 24 (1974).

(7) K. Yamauchi, T. Tanabe, and M. Kinoshita, *J. Org. Chem.*, 44, 638 (1979).

(8) Abbreviations used are the following: Ado, adenosine; 2'-MeAdo, 2'-*O*-methyladenosine; $N^6$-MeAdo, $N^6$-methyladenosine; 2',3'-$Me_2$Ado, 2',3'-di-*O*-methyladenosine; dAdo, deoxyadenosine; Guo, guanosine; Cyd, cytidine; Urd, uridine; 3-MeUrd, 3-methyluridine; dThd, thymidine. Similar notations are used for other nucleosides.

(9) D. J. Brown in "Mechanisms of Molecular Migrations", B. S. Thyagarajan, Ed., Interscience, New York, 1968, p 209.

(10) If one normalizes the data in Table I to 100% yield, so that the data portray relative distributions of products, the activity orders become $Mn^{2+} < Co^{2+} = Ni^{2+} < Zn^{2+} < Cu^{2+}$ for O'-methylation and $Mn^{2+} < Ni^{2+} < Co^{2+} < Zn^{2+} < Cu^{2+}$ for N-methylation. We express gratitude to a referee for pointing out the orders.

(11) H. Irving and R. J. P. Williams, *Nature (London)*, 162, 746 (1948); *J. Chem. Soc.*, 3192 (1953).

Table IV. Methylation of Various Nucleosides by $Me_3SOH$ in the Presence of $Cu(AA)_2$[a]

| nucleoside | product [% yield][b] |
|---|---|
| Cyd | 2′-MeCyd [60 (28)], 3′-MeCyd [22 (7)], 3-MeCyd [3 (13)] |
| 3-MeUrd | 3,2′-$Me_2$Urd [57 (31)], 3,3′-$Me_2$Urd [15 (8)], 3,2′,3′-$Me_3$Urd [12 (6)] |
| $N^6$-MeAdo | $N^6$,2′-$Me_2$Ado [37 (9)], $N^6$,3′-$Me_2$Ado [33 (3)], $N^6$,$N^6$,2′(3′)-$Me_3$Ado [6 (20)] |
| 1-MeGuo | 1,2′-$Me_2$Guo [38 (35)], 1,3′-$Me_2$Guo [47 (12)] |
| Guo | 1-MeGuo [16 (8)], 2′-MeGuo [18 (12)], 3′-MeGuo [17 (3)], 1,2′-$Me_2$Guo [15 (21)], 1,3′-$Me_2$Guo [12 (7)], $O^6$-MeGuo [2 (7)] |

[a] See footnote *a* of Table I for the reaction conditions. [b] Yields of products without the use of $Cu(AA)_2$ are shown in parentheses.

Our results differ from those obtained in Lewis acid catalyzed methylation of Ado with diazomethane,[2] where catalysts containing $Ni^{2+}$, $Cu^{2+}$, and $Zn^{2+}$ did not influence the reaction. Although $SnCl_2$ and $SnCl_4$ as well as $FeCl_2$ and $FeCl_3$ are good catalysts in this reaction, we could not investigate the effects of $Sn^{2+}$, $Sn^{4+}$, and $Fe^{2+}$ since their acetylacetone complexes could not be obtained as stable compounds.

Table II shows the results of methylation of Ado in the presence of various amounts of $Cu(AA)_2$. O′-Methylation occurred almost exclusively when the ratio of complex to Ado was ≥0.5. Similar results were obtained with $Fe(AA)_3$, as shown in Table III.

Table IV summarizes methylation of Cyd, 3-MeUrd, $N^6$-MeAdo, 1-MeGuo and Guo using $Cu(AA)_2$. Without the copper complex, the combined yields of 2′-*O*-methyl and 3′-*O*-methyl derivatives were less than 35–50%. The relative activities of other $M(AA)_n$ on O′-methylation were similar to those observed in the O′-methylation of Ado (Table I). It was found that most of $M(AA)_n$ suppressed methylation of Cyd at the N-3 position. By contrast, 3-MeCyd was produced in 13% yield in the absence of $M(AA)_n$. Thus, metal-catalyzed methylation of Cyd provided selectively 2′(3′)-*O*-methylcytidines.

None of the $M(AA)_n$ examined affected O′-methylation of deoxyribonucleosides (dAdo, dGuo, dCyd, dThd, and 3-MedThd) and O′-monomethylated ribonucleosides such as 2′-MeAdo, 3′-MeAdo, and 2′-MeCyd. However, methylation of their adenine rings at N-1 positions and of their cytosine rings at N-3 positions was suppressed in a degree similar to methylation of Ado and Cyd at these positions.

We suggest that the enhanced O′-methylation of these ribonucleosides by $M(AA)_n$ reflects the formation of a metal ion complex with the vicinal oxygen atoms of the 2′ and 3′ hydroxyls of the ribose moiety. It has been reported that $Cu^{2+}$ forms such complexes with ribonucleosides, shifting the $pK_a$ of the ribose hydroxyls down by about 2 pH units.[5] Consequently, trimethylsulfonium ion may attack these oxygens easily to form the 2′- and 3′-*O*-methyl derivatives in high yields. The formation of such a metal ion complex would also account for the approximately 1:1 ratio of 2′:3′ methyl derivatives formed in the presence of the most active ions, $Cu^{2+}$ and $Fe^{3+}$, compared with the 2.8:1 ratio formed in the absence of metal ions (cf. Tables II and III). This postulated action of metal ions is also consistent with our observation that these ions do not affect O′-methylation of deoxyribonucleosides, which cannot form such a complex.

The suppression of N-methylation may reflect in part competition for $Me_3SOH$ that is being used in the promoted O′-methylation. On the other hand, it has been shown that transition metal ions such as $Cu^{2+}$, $Zn^{2+}$, and $Mn^{2+}$ bind to adenine nucleosides at the N-1 or N-7 positions and to cytosine nucleosides at the N-3 position.[4] We consider that such ion binding at the N-1 and N-3 positions of the purine and pyrimidine rings could impede the attack of trimethylsulfonium ion at these positions; in addition, metal ion binding at the N-7 position of adenine nucleo-

Table V. Chromatographic Data, Melting Points, and UV Spectra of Principal Products

| compd | solvent[a] for column chromatography | mobility ($R_f$) in TLC[b] | | $\lambda_{max}$ (log $\epsilon$) at pH 7 | mp, °C (solvent for recrystallization) |
|---|---|---|---|---|---|
| 2′-MeAdo | A | 0.48 | 0.76 | 259 (4.14) | 202–203 (EtOH) (lit.[1] 202–203.5) |
| 3′-MeAdo | A | 0.48 | 0.76 | 259 (4.14) | 176–178 (EtOH) (lit.[1] 177–178) |
| $N^6$,2′-$Me_2$Ado | B | 0.57 | 0.85 | 266 (4.18) | 103–105 (acetone-*n*-hexane)[d] |
| $N^6$,3′-$Me_2$Ado | B | 0.57 | 0.85 | 266 (4.18) | 189–191 (acetone-*n*-hexane)[e] |
| 2′-MeCyd | C | 0.51 | 0.70 | 271 (3.95) | 251–253 (EtOH) (lit.[1] 251–254) |
| 3′-MeCyd | C | 0.51 | 0.70 | 271 (3.92) | 209–210 (EtOH) (lit.[1] 210–211) |
| 2′-MeGuo | *c* | 0.05 | 0.39 | 253 (4.15) | 231–233 (MeOH) (lit.[1] 234–236) |
| 3′-MeGuo | *c* | 0.05 | 0.39 | 254 (4.13) | 265 dec (lit.[1] 258 dec) |
| 1,2′-$Me_2$Guo | B | 0.26 | 0.73 | 254, 277[i] | *f* |
| 1,3′-$Me_2$Guo | B | 0.26 | 0.73 | 254 (4.04) 277[i] | 144–145 (acetone-diethyl ether)[e] |
| 3,2′-$Me_2$Urd | B | 0.29 | 0.87 | 262 (3.92) | 138–140 (*n*-hexane) (lit.[g] 140–141) |
| 3,3′-$Me_2$Urd | B | 0.29 | 0.87 | 262 (3.94) | 124–126 (*n*-hexane) (lit.[g] 125–127) |
| 3,2′,3′-$Me_3$Urd | B | 0.38 | 0.95 | 262 (3.93) | 105 (acetone-*n*-hexane)[h] |

[a] See the experimental section for solvent systems, column supports, etc. [b] Silica gel TLC (left $R_f$), solvent A for products of Ado, Guo, and Urd, solvent C for products of Cyd. Cellulose TLC (right $R_f$), solvent D. [c] Compounds were isolated according to the procedure reported (ref 1). [d] The HCl salt, mp 178–180 °C (M. J. Robins, M. MacCoss, and A. S. K. Lee, *Biochem. Biophys. Res. Commun.*, **70**, 356 (1976), reports mp 179–180 °C). [e] The elemental analysis gave correct values for C, H, and N. $N^6$,3′-$Me_2$Ado: NMR ($D_2O$) δ 2.95 (s, 3, $NCH_3$) and 3.63 (s, 3, $OCH_3$). 1,3′-$Me_2$Guo: NMR ($D_2O$) δ 3.48 (s, 3, $NCH_3$) and 3.60 (s, 3, $OCH_3$). Authentic samples of $N^6$,3′-$Me_2$Ado, 1,2′-$Me_2$Guo, and 1,3′-$Me_2$Guo were also used to determine the position of methyl groups. They were synthesized by the reaction of 3′-MeAdo with methyl iodide and the reactions of 2′-MeGuo and 3′-MeGuo with $Me_3SOH$, respectively (see ref 7 and 12 for the methods). [f] The compound was hygroscopic: mp ca. 80 °C; NMR ($D_2O$) δ 3.40 (s, 3, $NCH_3$) and 3.51 (s, 3, $OCH_3$); mass spectrum, *m/e* (relative intensity, 75 eV) 311 (M, 2), 222 (3), 166 (base + 2, 30), and 165 (base + 1, 100). The spectra were identical with those of an authentic sample, see footnote *e*. [g] Y. Furukawa, K. Kobayashi, Y. Kanai, and M. Honjo, *Chem. Pharm. Bull. (Tokyo)*, **13**, 1273 (1965). [h] The elemental analysis provided correct values for C, H, and N. NMR ($D_2O$) δ 3.36 (s, 3, $NCH_3$), 3.52 (s, 3,3′-$OCH_3$), and 3.60 (s, 3,2′-$OCH_3$); mass spectrum *m/e* (relative intensity, 75 eV) 286 (M, 30), 161 (sugar - 1, 100), 127 (base + 2, 95), and 226 (base + 1, 80). [i] Shoulder peak.

sides should have a similar effect by reducing the nucleophilicity at the N-1 position.

## Experimental Section

**Materials.** Ado, Cyd, Guo, and metal acetylacetonates [M(AA)$_n$] were commercially available. Authentic samples (1-MeAdo, $N^6$-MeAdo, 2',3'-Me$_2$Ado, 3-MeCyd, $O^6$-MeGuo, etc.) were prepared according to the literature[12,13] in order to identify minor products described in Tables I and IV. Synthesis of Me$_3$SOH was described previously.[7]

**Chromatographic Systems.** Thin-layer chromatography (TLC) was performed on silica gel ($GF_{254}$, type 60, Merck) and cellulose (Eastman chromagram sheet 13254). Dry-packed column chromatography was carried out with silica gel (Merck, art. 7734, 70–230 mesh). The following solvents were used for analysis of products. Silica gel: solvent A (chloroform–methanol, 17:3 v/v) for reaction products of Ado and dAdo; solvent B (chloroform–methanol, 15:1 v/v) for reaction products of 2'-MeAdo, $N^6$-MeAdo, and 3-MeUrd; solvent C (chloroform–methanol, 5:1 v/v) for reaction products of Cyd, dCyd, 2'-MeCyd, and 3'-MeCyd; solvent D (*n*-propanol–concentrated ammonium hydroxide, 3:1 v/v) for reaction products of Guo, dGuo, and 1-MeGuo. Ion-exchange chromatography was conducted with Dowex 1 × 2, 100–200 mesh, $OH^-$ form.

**Methylation Procedure.** A mixture of the nucleoside and a methanol solution of Me$_3$SOH in a round-bottomed flask was concentrated in the presence or absence of M(AA)$_n$, using a rotary evaporator. The residue was heated in DMF at 70 °C for 0.5–1 h with magnetic stirring in an atmosphere of nitrogen.

Most products were isolated by silica gel column chromatography. The first fraction gave M(AA)$_n$. The recovery of Cu(AA)$_2$ was particularly good (71–90%). Since 2'-*O*-methyl- and 3'-*O*-methylnucleosides were always eluted in the same fraction in the silica gel chromatography of the reaction mixture, their yield ratio was determined conveniently from the area ratio of the corresponding methoxy groups in the NMR spectrum of the mixture. The O'-methylated nucleosides were then resolved by ion-exchange chromatography according to the methods reported.[1,13]

A product distribution of the reaction mixture was determined easily as follows. A small portion of the reaction mixture in water was mixed with aqueous ammonium sulfide. The resulting metal sulfide was filtered and the solution was processed by the TLC–UV spectroscopic method reported previously.[14]

UV spectra at pH 1, 7, and 13 as well as melting points (mp) of all known isolated compounds agreed with literature values. Their NMR spectra were also coincided with the assigned structures. Compounds that were not isolated were identified by comparison of their mobilities in TLC using several solvents and by comparison of UV spectra (pH 1, 7, and 13) of aqueous extracts of the spots with those of authentic samples. Table V gives the chromatographic data, the melting points, and spectral data for principal products.

**Registry No.** Ado, 58-61-7; 2'-MeAdo, 2140-79-6; 3'-MeAdo, 10300-22-8; 1-MeAdo, 15763-06-1; $N^6$-MeAdo, 1867-73-8; $N^6$,2'-Me$_2$Ado, 57817-83-1; $N^6$,3'-Me$_2$Ado, 60037-52-7; 2',3'-Me$_2$Ado, 20649-46-1; Cyd, 65-46-3; 2'-MeCyd, 2140-72-9; 3'-MeCyd, 20594-00-7; 3-MeCyd, 2140-64-9; 3-MeUrd, 2140-69-4; 3,2'-Me$_2$Urd, 7103-27-7; 3,3'-Me$_2$Urd, 7103-28-8; 3,2',3'-Me$_3$Urd, 53657-36-6; $N^6$,$N^6$,2'-(3')-Me$_3$Ado, 74466-63-0; 1-MeGuo, 2140-65-0; 1,2'-Me$_2$Guo, 73667-71-7; 1,3'-Me$_2$Guo, 74466-66-3; Guo, 118-00-3; 2'-MeGuo, 2140-71-8; 3'-MeGuo, 10300-27-3; $O^6$-MeGuo, 7803-88-5; $N^6$,2'-Me$_2$Ado·HCl, 59867-23-1; Me$_3$SoH, 17287-03-5; [Mn(AA)$_2$], 14024-58-9; [Co(AA)$_2$], 14024-48-7; [Zn(AA)$_2$], 14024-63-6; [Ni(AA)$_2$], 3264-82-2; [Cu(AA)$_2$], 13395-16-9; [Fe(AA)$_3$], 14024-18-1.

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# Acylanthranils. 10. Influence of Hydrogen Bonding on Hydrolysis of Acetylanthranil in Organic Solvents

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The hydrolysis of acetylanthranil (**1**) to give *o*-acetamidobenzoic acid (**2**) in organic solvents at room temperature was monitored by proton NMR and/or gravimetrically. The results show that the second-order rate constant in benzene is about equal to that in water at pH 6.8. The corresponding rate constant for hydrolysis by a stoichiometric amount of water in proton-acceptor solvents decreases in the order benzene > dimethyl-$d_6$ sulfoxide > acetone-$d_6$ > dimethylformamide-$d_7$ > pyridine, and for hydrolysis in proton donor solvents, it decreases in the order benzene > chloroform-*d* > acetonitrile-$d_3$. The observed second-order rate "constant" in organic solvents, however, is not a true constant, since it increases linearly with water concentration. It was observed also that the plots of log [$H_2O$]/[**1**] as a function of time, *t*, show an inflection at some time, $t_i$, that appears to correspond to a critical equilibrium concentration of available proton from the acid product **2**. The magnitude of $t_i$ is decreased considerably by addition of **2** at time zero, and it is eliminated completely by addition of HCl. On the other hand, it is increased considerably by addition of solutes that are strong proton acceptors, such as 1,8-bis(dimethylamino)naphthalene or 1,4-diazabicyclo[2.2.2]octane. These results are consistent with the hypothesis that hydrolysis of **1** in organic solvents involves interaction with molecular clusters of water such as $(H_2O)_n$ in benzene, S·HOH·S or $(HOH·S)_n$ in proton-acceptor solvents, S, and $H_2O$·HS in proton donor solvents, SH.

## Introduction

In our preceding paper,[1] we reported that the results observed when acetylanthranil (**1**) is made to react with ammonia in organic solvents are consistent with the premise that the nucleophile reacts with **1** as a molecular cluster rather than as an individual molecule and that the mechanism involves association of the cluster by hydrogen bonding with the heterocyclic nitrogen of **1** to form a mixed complex followed by nucleophilic attack at C-2 or C-4, depending on the reaction conditions. We noted that the addition of a small amount of water to these systems caused a sharp change in selectivity and an enormous

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