Determination of Hydroxy Compounds by 4-Dimethylaminopyridine-Catalyzed Acetylation

KENNETH A. CONNORS[▲] and KENNETH S. ALBERT

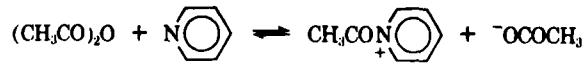
Abstract □ 4-Dimethylaminopyridine is an effective catalyst of analytical acylations by acetic anhydride, having a specific catalytic activity about 10^4 times greater than that of pyridine. The conventional titrimetric determination of hydroxy groups is carried out with 4-dimethylaminopyridine as the catalyst and pyridine as the solvent. Typical reaction times for primary and secondary alcohols are 5–10 min. at 54–70°.

Keyphrases □ *Hydroxy compounds—determination* by 4-dimethylaminopyridine-catalyzed acetylation, compared to pyridine catalysis □ Alcohols—4-dimethylaminopyridine-catalyzed acetylation, titrimetric determination, compared to pyridine catalysis □ 4-Dimethylaminopyridine—as a catalyst of acylations by acetic anhydride, titrimetric determination of hydroxy compounds

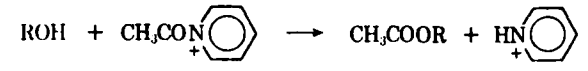
Pyridine-catalyzed acetylation (1) and phthalation (2) are standard methods for the determination of hydroxy compounds and other acylable substances. The mechanism involves nucleophilic catalysis with the intermediate formation of the acylpyridinium ion (3), as shown in Schemes I and II for the reaction of an alcohol with acetic anhydride.

Although pyridine is an effective catalyst in such acylations, typical reaction times are 0.5–1 hr. at reflux temperature. Schenk *et al.* (4) compared several tertiary amines as catalysts in the acetylation of cyclohexanol; they found that triethylenediamine is about 50 times more effective than pyridine. Because of the greater base strength of this saturated amine, it was necessary to modify the classical titrimetric finish (4). Triethylenediamine is also a better catalyst than is pyridine in the acylation of alcohols with the acid chloride of the 2,4-dinitrophenylhydrazone of pyruvic acid (5). Imidazole catalyzes acylations by pyromellitic dianhydride (6). Analytical acylations were thoroughly reviewed by Mehlenbacher (7) and Schenk (8).

Recently, Steglich and Höfle (9) reported that 4-dimethylaminopyridine is superior to pyridine as a catalyst for some synthetic acylations. The present article describes the application of 4-dimethylaminopyridine (I) to the determination of hydroxy compounds by reaction with acetic anhydride.



Scheme I



Scheme II

EXPERIMENTAL

Materials—4-Dimethylaminopyridine[1] was used directly.

Reagents—*Acetic Anhydride Solution*—Ten milliliters of reagent grade acetic anhydride was mixed with 40 ml. of reagent grade pyridine. This reagent should be prepared fresh daily.

Catalyst Solution—Two grams of 4-dimethylaminopyridine was dissolved in enough pyridine to make 100 ml. Each 5-ml. aliquot of this solution contained 100 mg. of I.

Procedure—A 2–3-meq. sample of a hydroxy compound contained in 1.0 ml. of pyridine solution was pipeted into a 50-ml. conical flask. Five milliliters of the catalyst solution, followed by 2.0 ml. of the acetic anhydride solution, was added, and the solution was well mixed. The stoppered flask was maintained at the selected temperature for an appropriate time (see Table I and *Results and Discussion*). Then 25 ml. of water was added to the flask and the contents were brought to room temperature. If the mixture was not homogeneous, 5 ml. of *n*-butyl alcohol was added. Three drops of 1% phenolphthalein solution was added, and the solution was titrated to the pink color with standard 0.5 *N* sodium hydroxide. A blank determination, omitting only the sample, was carried out in exactly the same way.

The milliequivalents of hydroxy compound contained in the sample taken for assay is given by $N(V_b - V_s)$, where V_b and V_s are the volumes (in milliliters) of sodium hydroxide solution of normality N required to titrate the blank and sample, respectively.

RESULTS AND DISCUSSION

Figure 1 shows the time course for acetylation of isopropyl alcohol in a pyridine–acetic anhydride mixture at different concentrations of I. A profound catalysis of this esterification by I clearly occurs. In the development of the analytical procedure, pyridine has been retained as the solvent, although it makes little contribution to the overall catalysis.

An estimate of the relative catalytic efficiencies of I and pyridine (II) was obtained as follows. It is anticipated that the rate for acylation in a I–pyridine–acetic anhydride mixture will be given by Eqs. 1–3:

$$v = (k_{\mathrm{I}}[\mathrm{I}] + k_{\mathrm{II}}[\mathrm{II}])[\mathrm{ROH}][(\mathrm{CH_3CO})_2\mathrm{O}] \quad \text{(Eq. 1)}$$

$$v = (k_{\mathrm{I}}' + k_{\mathrm{II}}')[\mathrm{ROH}][(\mathrm{CH_3CO})_2\mathrm{O}] \quad \text{(Eq. 2)}$$

$$v = k_{\mathrm{obs}}[\mathrm{ROH}][(\mathrm{CH_3CO})_2\mathrm{O}] \quad \text{(Eq. 3)}$$

Table I—Analytical Results of 4-Dimethylaminopyridine-Catalyzed Acetylation of Hydroxy Compounds

Sample Compound	Amount[a] I, mg.	Temperature	Reaction Time, min.	Percent Recovery—Mean[b]	Percent Recovery—*SD*
n-Propyl alcohol	50	54°	20	100.1	0.2
Isopropyl alcohol	50	54°	20	100.1	0.4
Benzyl alcohol	50	54°	20	100.4	0.6
n-Butyl alcohol	100	54°	10	99.0	0.5
Phenol	100	54°	10	101.2	0.3
Cinnamyl alcohol	100	54°	10	98.1	0.4
Isobutyl alcohol	100	70°	5	100.6	0.4
Ethylene glycol[c]	100	70°	5	99.2	0.2
p-Methoxyphenol[d]	100	70°	10	99.4	—

[a] Amount of I in the 8-ml. reaction volume. [b] Mean of three determinations except as noted. [c] Both hydroxy groups acetylated. [d] Two determinations.

[1] Aldrich Chemical Co. A sample of I recrystallized from Skellysolve A gave the same results. It has been found convenient to refer to I as DMAP.

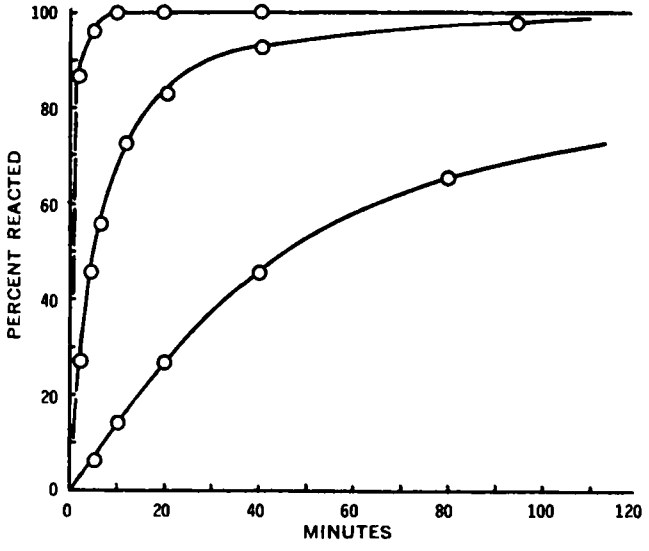
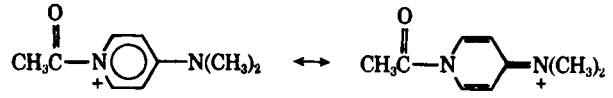


Figure 1—*Time course for acetylation of isopropyl alcohol by acetic anhydride at 54° and varying I concentration. The solvent was acetic anhydride–pyridine (1:4 v/v). Compound I concentrations (slowest to fastest reactions) were: zero, 4.65 × 10⁻³, and 4.48 × 10⁻² M.*

From the titrimetric data, the apparent second-order rate constant, k_{obs}, could be obtained. The plots showed some deviations from strict second-order kinetics, but for the present purpose it was possible to obtain these estimates: for reaction with isopropyl alcohol at 54°, $k_{II} = 3.6 \times 10^{-6}\ M^{-2}$ sec.$^{-1}$ and $k_I = 7 \times 10^{-2}\ M^{-2}$ sec.$^{-1}$. Therefore, I is about 2×10^4 times more effective than is pyridine as a catalyst in this reaction. This rate enhancement may be a consequence of stabilization of the acylpyridinium ion, or rather of the transition state leading to it, as shown in Scheme III.

Table I lists analytical results for the I-catalyzed acetylation of various hydroxy compounds. The accuracy and precision of the method are comparable with those of other acylation procedures. Given a sample compound, the analyst has available for manipulation three experimental variables: I concentration, temperature, and reaction time. Sufficient variation in these quantities is represented in Table I for the analyst to select appropriate conditions to suit his or her requirements. The attempted determination of *tert*-butyl alcohol (100 mg. I, 70°) gave 26% acetylation in a 75-min. reaction time.



Scheme III

A yellow color in the presence of high I concentrations limits the accuracy of the visual end-point detection. In the procedure as described, it appears that 100 mg. of I in the 8-ml. assay volume is about the maximum practical amount. Higher concentrations of I give increasingly erratic results, which are associated with definite consumption of reagent even in the blank solution. Possibly this very powerful catalyst is promoting C-acylation of acetic anhydride in a Perkin-type reaction.

The 4-dimethylaminopyridine-catalyzed method given here appears to be the most reactive of available anhydride acylation methods utilizing nucleophilic catalysis. Extension of 4-dimethylaminopyridine catalysis to other acylating agents, types of samples, and finish methods should be analytically fruitful.

REFERENCES

(1) C. L. Ogg, W. L. Porter, and C. O. Willits, *Ind. Eng. Chem., Anal. Ed.*, **17**, 394(1945).

(2) P. J. Elving and B. Warshowsky, *ibid.*, **19**, 1006(1947).

(3) A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, **91**, 2125(1969).

(4) G. H. Schenk, P. Wines, and C. Mojzis, *Anal. Chem.*, **36**, 914(1964).

(5) D. P. Schwartz, *Anal. Biochem.*, **38**, 148(1970).

(6) B. H. M. Kingston, J. J. Garey, and W. B. Hellwig, *Anal. Chem.*, **41**, 86(1969).

(7) V. C. Mehlenbacher, *Org. Anal.*, **1**, 1(1953).

(8) G. H. Schenk, "Organic Functional Group Analysis," Pergamon Press, Oxford, England, 1968, chaps. 3 and 4.

(9) W. Steglich and G. Höfle, *Angew. Chem. Int. Ed.*, **8**, 981 (1969).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 30, 1972, from the *School of Pharmacy, University of Wisconsin, Madison, WI 53706*

Accepted for publication December 6, 1972.

▲ To whom inquiries should be directed.