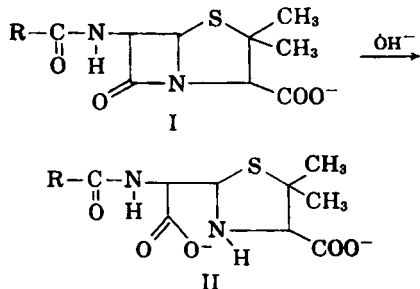


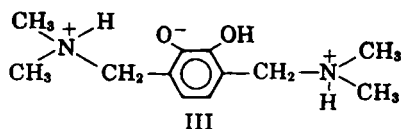
Catalysis of Penicillin Hydrolysis by Catechol and 3,6-Bis-(dimethylaminomethyl)catechol

Sir:

Penicillins (I) are hydrolyzed to penicilloic acids (II) by hydroxyl ion and by the enzyme penicillinase (1). It has now been found that this



reaction is also catalyzed by catechol and even more markedly by 3,6-bis(dimethylaminomethyl)catechol (CDM).¹ The rates of penicillin hydrolysis were measured by following the acid produced by the reaction with a recording pH-stat. The rates were pseudo first order at constant pH; Fig. 1 shows the dependence upon pH of the rate of hydrolysis of penicillin G (R = C₆H₅CH₂-) in the presence or 1.33 × 10⁻³ M CDM dihydrochloride at 31.5°. This bell-shaped curve with maximum at pH 8.0 is consistent with catalysis by the species III, the monoanion of the dihydrochloride. That III is the monoanion



is evidenced by the pK_a of 6.35 and 9.65 obtained by potentiometric titration and the bathochromic shift in the ultraviolet absorption maximum noted after neutralization of 1 proton of the dihydrochloride. The latter is typical of phenolic ionization (2). In the case of catechol, the pH dependence of the reaction also showed that the monoanion was the reactive species. Catalytic second-order rate constants for the reaction of the following species with penicillin G at 31.5° were (liter mole⁻¹ minute⁻¹): hydroxyl ion, 12.5; monocatechol ion, 3.8; and species III, 54.0. Based on these constants, the half-life of penicillin

¹ This compound was originally synthesized by Dr. J. Epstein and co-workers, U. S. Army Chemical Center, Edgewood, Md., and is highly reactive with phosphonofluoridates. It is expected that their synthesis will be published shortly.

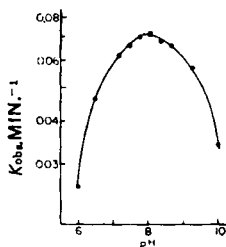


Fig. 1.—Dependence upon pH of observed pseudo first-order rate constants (log scale) for hydrolysis of benzyl penicillin catalyzed by CDM. Concentration of penicillin was 0.002 M; CDM was 0.00133 M.

lin G in aqueous solution at pH 8 would be approximately 575 hours² with no catalyst added, about 25 hours in the presence of 0.001 M catechol, and only 13 minutes in the presence of 0.001 M CDM.

In the past, monocatechol ion has been shown to be an effective catalyst for hydrolysis of phenyl chloroacetate (3) and to react unusually rapidly with isopropyl methylphosphonofluoridate (sarin) (4). In both cases the *ortho* acidic hydroxyl group was necessary for enhanced reactivity. It has also been demonstrated that aminoalkyl groups increase the reactivity of phenol with sarin (5) and the rate of catalysis of *p*-nitrophenyl acetate hydrolysis by imidazole (6). In the latter case, the rate enhancement was attributed to polarization of the ester carbonyl by the charged amine, thus increasing the electrophilicity of the carbonyl carbon.

In the present case, where both an acidic *ortho* hydroxyl group and a charged aminoalkyl group are present, it seems likely that both may be involved in the reaction. Further work is underway to elucidate the mechanism of this catalysis and will be reported at a later date. There is some evidence that the nature of the side chain of the penicillin (R in I) plays a role. It seems probable from past work that CDM will also catalyze the hydrolysis of certain esters; this is also being investigated.

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MICHAEL A. SCHWARTZ

Department of Pharmaceutics
School of Pharmacy
State University of New York at Buffalo
Buffalo

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² This half-life was computed on the basis of alkaline hydrolysis only. The actual half-life will be somewhat shorter due to a spontaneous hydrolysis which is also known to occur.