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ARTICLE *in* JOURNAL OF THE CHEMICAL SOCIETY CHEMICAL COMMUNICATIONS · JANUARY 1979

DOI: 10.1039/c39790000298

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Intramolecular General Acid Catalysis in the Aminolysis of Benzylpenicillin. A Preferred Direction of Nucleophilic Attack

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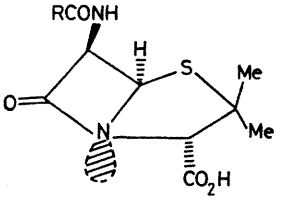
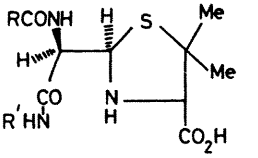
Summary The reaction of 1,2-diaminoethane monocation with benzylpenicillin shows a rate enhancement of *ca.* 100-fold compared with a monoamine of similar basicity; this is attributed to intramolecular general acid catalysis which in turn indicates that nucleophilic attack takes place from the least hindered α-side in disagreement with the prediction of the theory of stereoelectronic control.

THE reaction of amines with penicillins (**1**) to form penicilloyl amides (**2**) requires at least two proton transfers, proton removal from the attacking amine and proton addition to the β-lactam nitrogen. The importance of proton removal is manifested by the dominance of general base catalysis in the rate law for the aminolysis of penicillins.[1] In contrast, general acid catalysis involving proton transfer to the β-lactam nitrogen makes no detectable contribution to the rate of aminolysis with simple primary monoamines.[1,2] We report here evidence for intramolecular general acid catalysis in the aminolysis of benzylpenicillin with 1,2-diaminoethane monocation.



(1)



(2)

It is well known that the direction of nucleophilic addition to the carbonyl group may be dominated by steric effects[3] and, according to a recent theory,[4] stereoelectronic factors may also be important. Nucleophilic

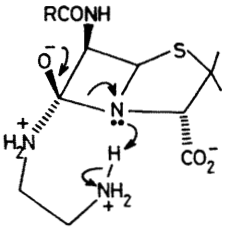
substitution at the carbonyl centre is thought to proceed through the formation of a tetrahedral addition intermediate.[5] According to the theory of stereoelectronic control of Deslongchamps[4] the breakdown of such tetrahedral intermediates is facilitated by the lone pair of the heteroatoms attached to the incipient carbonyl carbon being antiperiplanar to the leaving group. Application of this theory to the microscopic reverse steps predicts that the direction of nucleophilic attack on the carbonyl carbon is such that the lone pairs on the heteroatoms will be antiperiplanar to the attacking group.

The penicillins (**1**) have a fairly rigid structure because of the fusion of the β-lactam and the thiazolidine rings giving a V-shaped molecule.[6] The β-lactam nitrogen is consequently prevented from adopting the sp^2 hybridisation found in normal amides and this is thought to reduce the conjugation between the nitrogen lone pair and the carbonyl group.[7] Another consequence of the non-planarity of the fused bicyclic ring system is that the electron density of the lone-pair of the β-lactam nitrogen will be concentrated heavily on the α-face of the penicillin molecule (**1**). According to the theory of stereoelectronic control[4] nucleophilic attack on penicillins should therefore take place from the β-side. However, this face is sterically hindered and we have previously suggested that nucleophilic attack may therefore take place from the α-side.[8] We report here evidence that suggests attack on benzylpenicillin probably takes place from the least hindered α-side.

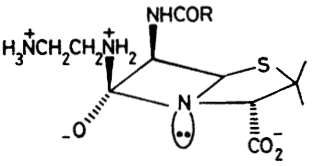
The rate law for the aminolysis of the sodium salt of benzylpenicillin in water at 30 °C is given by equation (1), where k_{obs} is the observed pseudo first-order rate constant and k_0 is the first-order rate constant for the hydrolysis reaction.[1] The individual rate constants were determined

$$k_{obs} = k_0 + k_1[RNH_2] + k_2[RNH_2]^2 + k_3[RNH_2][OH^-] \quad (1)$$

using the amine as both buffer and reactant.[1] The rate constant k_1 may represent either an uncatalysed or a water-catalysed reaction of the amine with penicillin. The rate constant k_1 for the monocation of 1,2-diaminoethane, obtained from measurements in buffer solutions of the mono- and di-cation, is $1{\cdot}36 \times 10^{-3}$ l mol^{-1} s^{-1}. This number is *ca.* 100 fold greater than that predicted from the Brønsted plot of the k_1 values for a series of amines,[1] for a monoamine of the same basicity as $^+NH_3CH_2CH_2NH_2$. The rate enhancement is attributed to intramolecular general acid catalysis of aminolysis by the protonated amine. There is good evidence that the aminolysis of benzylpenicillin proceeds through the formation of a tetrahedral intermediate in which the bond to the attacking amine is made before the β-lactam carbon–nitrogen bond is broken.[8,9] Breakdown of the intermediate (**3**) formed from the monocation of 1,2-diaminoethane and benzylpenicillin may be facilitated by proton donation from the terminal protonated amino group to the β-lactam nitrogen. We make no comment at this stage on the relative timing of proton transfer and carbon-β-lactam nitrogen bond fission.



(3)



(4)

The mechanism depicted in (**3**) implies a different pathway to that generally used in the aminolysis of penicillin which involves proton abstraction from the attacking amino group.[1,8,9] Although the mechanism suggested in (**3**) indicates the formation of the unstable *N*-protonated amide product this is also thought to occur in the aminolysis of acetylimidazole.[8] The driving force for expulsion of the imidazole anion is less than in the case of (**3**) which is also facilitated by a release of strain energy upon ring opening.

In order that ready proton transfer takes place from the protonated amine to the β-lactam nitrogen it is essential that the tetrahedral intermediate (**3**) has the geometry shown. Although intramolecular general acid catalysis could conceivably take place if the amine attacked from the β-face, to give the tetrahedral intermediate (**4**), this would involve considerable non-bonded interactions and/or the proton transfer taking place through one or more water molecules. Further evidence for nucleophilic attack taking place from the α-face comes from the *absence* of intramolecular general base catalysis in the aminolysis of 6β-aminopenicillanic acid.[9] That the lone pair on the β-lactam nitrogen takes up the geometry shown is supported by the observation that copper(II)-ions catalyse the aminolysis of penicillin by co-ordination to the β-lactam nitrogen and the carboxy group, thus stabilising the tetrahedral intermediate.[10,11] Thus, nucleophilic attack on penicillins, at least by amines, appears to take place from the least hindered side in contrast to the prediction of the theory of stereoelectronic control.[4]

We thank the S.R.C. for a grant and Southern E.L.B., Armagh (A.F.M.) and Kirklees M.C. (J.J.M.) for support.

(*Received*, 1*st December* 1978; *Com.* 1285.)

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