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NEUTRAL HYDROLYSIS REACTION OF ACETYL 1-HYDROXYBENZOTRIAZOLE[1]

Kusuo Horiki
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, 553 Japan

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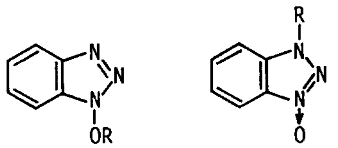
The very recent report of the hydrolysis of acylated 1-hydroxybenzotriazole (HOBt) by McCarthy et al.[2] prompted us to describe on our results on the hydrolysis of acetyl HOBt as our conclusions are very different.

Our preceding paper reported that HOBt esters of various N-protected amino acids exist in an equilibrium of two isomers (1a and 2a) when dissolved in dioxane and THF, and that two acetyl isomers (1b and 2b) can be successfully isolated. König and Geiger[3] have reported that



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a: R = R'OC(=O)-NHCH(R)CO-
b: R = CH_3CO-
c: R = H

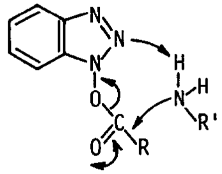


Fig. 1. Six-membered intramolecular general base catalysis proposed by König and Geiger.[3]

aminolysis of these HOBt esters of N-protected amino acids proceeds very rapidly even at low temperature and to account for this high reactivity, they postulated that the neighboring nitrogen general base catalysis shown in Fig. 1 might be responsible, without presenting any definite evidence.

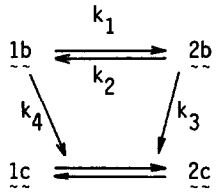
More recently, Sacher et al.[4] also reported a good linear free-energy relationship between anticholinesterase activity and the substituent effects of HOBt methyl- and dimethylcarbamates, which were investigated due to their high reactivities. The mechanism postulated by König and Geiger[3] seems attractive because a large number of investigations have shown that for the serine protease and/or its model reaction, imidazole nitrogen plays an important role as a general base catalyst for the acylated enzyme hydrolysis.[5]

On the other hand, Gandour[6] has recently proposed that the intramolecular proton transfer occurs with the highest probability when the cyclic transition states formed can accomodate a linear donor-acceptor arrangement of appropriate length, based on many examples. He concluded that the best situation for this is an eight-membered transition state without much strain.

Now, if the postulate of König and Geiger[3] is correct, 1a might be expected to undergo aminolysis much faster than 2a due to the difficulty of forming the five-membered cyclic transition state in which much strain might be involved. Therefore, it seems appropriate to study the kinetics of the aminolysis reaction for the two isomers (1a and 2a) in order to

determine whether an intramolecular general base catalysis is involved. However, the aminolysis of the acylated HOBt is too rapid even at low temperature to measure the rates as suggested by König and Geiger. We, therefore, used a neutral hydrolysis reaction[7] of acetyl HOBt as a model for the aminolysis reaction.

1-Acetoxybenzotriazole (1b) was chosen as the starting material. The reaction was carried out in 40% aqueous acetonitrile (v/v)[8] at 25°C. The total amount of residual acetyl HOBt (1b and 2b) at appropriate times was determined by converting them into acetohydroxamic acid[9] and the composition of each isomer (1b and 2b) was determined by nmr as described in the preceding paper in independent experiments under the same conditions. The color yield of both isomers for the acetohydroxamic acid determination using each pure compound exhibited the same calibration curve. The following rate constants using 1b were obtained graphically by the procedure of Yamana et al.[10]: 2.2×10^{-2} for k_1, 1.9×10^{-2} for k_2, 3.6×10^{-3} for k_3, and 9.5×10^{-3} min^{-1} for k_4, respectively in the Scheme. A small rate difference was observed between 1b and 2b.



Scheme

From our results, we can readily obtain the equilibrium constant (K = 2b/1b) of 1.3 using the equation derived by Alberty and Miller,[11] which agrees with the observed value (1.3). According to Boyle and Jones,[12] HOBt exists in a polar N-oxide form (2c) predominantly in the aqueous phase in contrast to the existence in a non-polar N-hydroxy form (1c) in ethanol. For an approximate comparison of the rates with pKa values of each isomer, which indicate the leaving ability, each pKa[13] in water was calculated giving 7.1 for 1c and 7.8 for 2c, although the present hydrolysis was carried out in 40% aqueous acetonitrile solution.

The pseudo-first-order rate constants for both isomers (1b and 2b) may be expressed as the following rate equation.[14]

$$k_{obs} = k_0 + k_{OH^-}[OH^-]$$

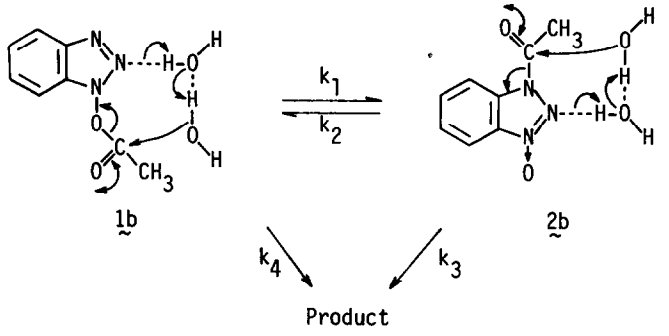
k_0: pH-independent hydrolysis rate constant

k_{OH^-}: second-order rate constant for hydroxide ion attack

Each spontaneous (pH-independent) rate constant (k_0) of 1b and 2b should be compared to determine the presence or absence of intramolecular catalysis in 1b because no such a catalysis is anticipated for 2b, as discussed above. However, as there is a lack of available data on k_0, it is difficult to discuss whether an intramolecular general base catalysis occurs for 1b.[14] The fact that both isomers of HOBt (1c and 2c) have similar pKa values in aqueous solution and similar k_{obs} values suggests that both acetates (1b and 2b) might be active enough to undergo neutral hydrolysis. This result is in marked contrast to that of McCarthy et al.[2] who could not isolate one of the isomers (2b). In order to explain why both acetyl compounds (1b and 2b) underwent neutral hydrolysis in the present investigation, two alternative pathways can be considered as shown in Fig. 2.

In spite of their having pKa similar to that of p-nitrophenol (pKa 7.16),[16] the larger rate constants of 1b and 2b than that of p-nitrophenyl acetate[17] can be explained satisfactorily by path a by taking into consideration Gandour's hypothesis,[6] where intramolecular general

Path a. Intramolecular general base catalysis.



Path b. Intermolecular general base catalysis.

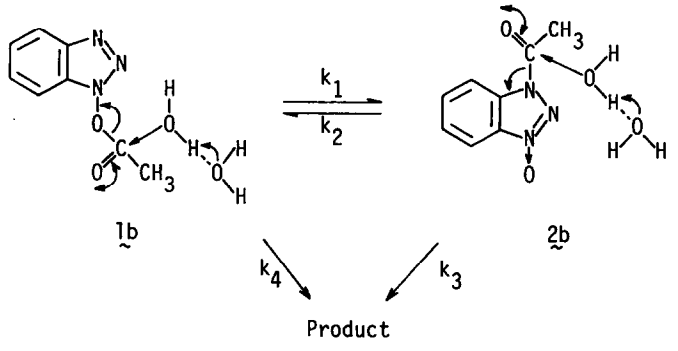
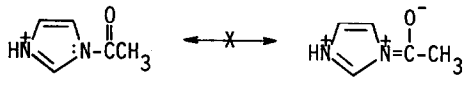


Fig. 2

base catalysis can operate effectively for both 1b and 2b. However, based on the excellent Brønsted plot including water reported by McCarthy et al.,[2] path b can not be ruled out and may even be preferable. Therefore, a larger rate constant of 1b than that of p-nitrophenyl acetate can be explained by the same reason given by McCarthy et al.[2] and that of N-acetyl derivative (2b) by the polarized N-oxide structure, similar to acetylimidazolium ion (a) in which the lone pair of nitrogen electrons can not participate in the resonance form (b).[18] However, a definite conclusion requires further data.



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7. The term "neutral hydrolysis reaction" is used to describe the spontaneous reaction in the absence of added acid or base and does not imply reaction at controlled pH. Cf. G. D. Cooper and B. Williams, J. Org. Chem. 27, 3717 (1962).
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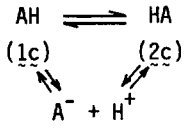

Our calculated values differ slightly from those reported in ref. 2.

14. This equation was obtained by Ravaux et al.[15] for the hydrolysis of N-acetylbenzotriazole and by McCarthy et al.[2] for the hydrolysis of 1-acyloxybenzotriazole. In the neutral region, the value of k_{obs} is close to that of k_0, although it is a crude estimation.
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