The Mechanism of General Acid Catalysis of the Aminolysis of an Amide[1]

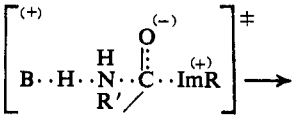
Sir:

We wish to report evidence that the proton transfer in the general acid catalyzed aminolysis of acetylimidazole involves the less basic of the attacking and leaving amines.

The site at which proton transfer takes place in general acid–base catalyzed reactions is a basic mechanistic problem that has been resolved for several carbonyl group and a few acyl group reactions.[2] We have used the model compound 1-acetyl-3-methylimidazolium chloride (AcImMe$^+$), in which a methyl group is substituted for the mobile proton of acetylimidazolium ion (AcImH$^+$), to examine this question in amide aminolysis; this compound has been used previously to demonstrate that uncatalyzed reactions of nucleophilic reagents with acetylimidazole take place predominantly by way of the acetylimidazolium ion.[3] General acid catalysis of the hydroxylaminolysis of simple amides has been demonstrated previously, but it was not possible to specify the site of catalysis with certainty.[4]

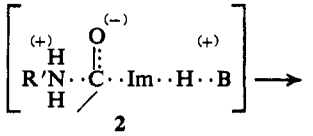
Two mechanisms for (kinetic) general acid catalysis of the aminolysis of acetylimidazole are shown in eq 1 and 2; catalysis by both mechanisms follows the rate law[5] of eq 3. Mechanism 1 involves reaction of the

$$B + R'NH_2 + \overset{+}{AcImR} \rightleftharpoons$$



$$\mathbf{1} \qquad \overset{+}{BH} + R'NHAc + ImR \quad (1)$$

$$R'NH_2 + AcIm + \overset{+}{HB} \rightleftharpoons$$



$$\mathbf{2}$$

$$R'NHAc + ImH + \overset{+}{HB} \quad (2)$$

$$v = k[RNH_2][AcImH^+][B] = k'[RNH_2][AcIm][BH^+] \quad (3)$$

acetylimidazolium ion with assistance by proton removal from the attacking amine by a general base catalyst. Mechanism 2 involves general acid catalysis by proton donation to the leaving imidazole group. We take no position at this time regarding the possible formation of a tetrahedral addition intermediate; if such an intermediate exists, catalysis according to mechanism 1 or 2 could involve either formation or breakdown of the intermediate. If mechanism 1 is correct

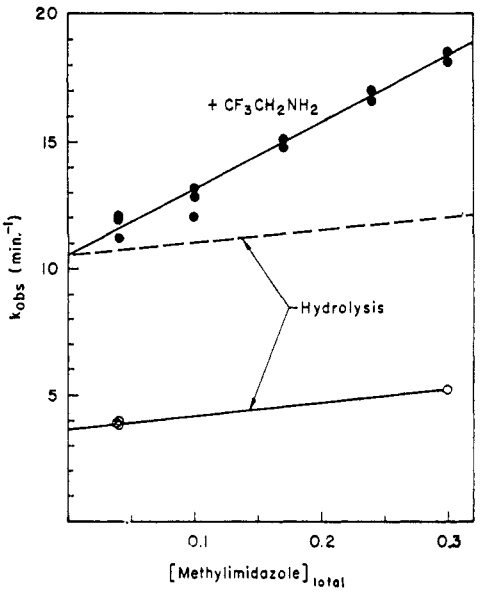


Figure 1. Catalysis by methylimidazole buffer, 30% base, of the reaction of acetylmethylimidazolium ion[3] with 0.045 *M* trifluoroethylamine and with water at 25°, ionic strength maintained at 0.3 with tetramethylammonium chloride, followed at 250 nm.

then AcImMe$^+$ should be a model for AcImH$^+$, as it is in the uncatalyzed reaction,[3] and catalysis should be observed with this compound; if mechanism 2 is correct no catalysis should be observed because the leaving group of AcImMe$^+$ is already cationic and mechanism 2 is not possible.

Experimentally, no methylimidazole catalysis is observed of the ammonolysis of AcImMe$^+$ (0.02 *M* total ammonia, ionic strength 0.2, 0–0.2 *M* methylimidazole buffer, 50% base, 25°); the observed rate increase of 1.6 min^{-1} (from 12.2 to 13.8 min^{-1}) is accounted for entirely by buffer catalysis of hydrolysis.[3] The observed catalysis of acetylimidazole ammonolysis by imidazole[5] (k' = 1700 M^{-2} min^{-1}, k = 3.0 × 10^6 M^{-2} min^{-1}) would require a rate increase of 89 min^{-1} under these conditions if this catalysis occurred according to mechanism 1. Similarly, no catalysis was observed of the aminolysis of AcImMe$^+$ by ethylamine (0.01 *M* ethylamine, 0–0.3 *M* methylimidazole buffer, 40% base; calcd rate increase based on acetylimidazole = 12–16 min^{-1} for mechanism 1). Thus, the data rule out mechanism 1 but are consistent with mechanism 2 for the imidazole-catalyzed aminolysis of acetylimidazole by strongly basic amines.

However, since the aminolysis of an amide is a symmetrical reaction one might expect that when the attacking amine is a *weaker* base than the leaving group, catalysis might involve proton transfer at the other end of the system according to mechanism 1; if this were the case AcImMe$^+$ would be a model for the reaction of acetylimidazole and catalysis of AcImMe$^+$ aminolysis should be observed. In agreement with this prediction the aminolysis of AcImMe$^+$ by trifluoroethylamine (pK = 5.8) is catalyzed by methylimidazole (Figure 1). The catalytic rate constant, k, of 1560 M^{-2} min^{-1} agrees well with that of 1780 M^{-2} min^{-1} calculated for the observed catalysis of the aminolysis of acetylimidazole by imidazole, so that the latter catalysis may be accounted for by mechanism 1 without any significant contribution from mechanism 2. The

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(2) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969.

(3) R. Wolfenden and W. P. Jencks, *J. Amer. Chem. Soc.*, 83, 4390 (1961).

(4) W. P. Jencks and M. Gilchrist, *ibid.*, 88, 104 (1966).

(5) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, 234, 1272, 1280 (1959).

reaction of $AcImMe^+$ with methoxyamine ($pK = 4.7$) is also catalyzed by methylimidazole (0.002 M methoxyamine, other conditions as in Figure 1) and the observed catalytic constant ($k = 46{,}400\ M^{-2}\ min^{-1}$) is sufficient to account for most or all of the imidazole-catalyzed methoxyaminolysis of $AcImH^+$ ($k = 59{,}000\ M^{-2}\ min^{-1}$) according to mechanism 1.

These results suggest that the breakdown of the symmetrical transition state or intermediate, with two amines bonded to the acyl carbon atom, involves proton donation by a general acid catalyst to the more weakly basic amine. Mechanisms involving proton transfer to or from the carbonyl oxygen atom are less likely in view of the symmetry of the reaction and its catalysis as well as the fact that $AcImMe^+$ is a satisfactory model for the general base catalyzed reactions of weakly basic amines and for the uncatalyzed reactions of a number of other nucleophiles with acetylimidazole near neutrality;[3,6] *i.e.*, protonation of the leaving imidazole by either specific or general acid catalysis is the preferred pathway for reactions of acetylimidazole. These reactions may be interpreted in the following way, according to the expected structure–reactivity relationships and the notion that catalysis occurs where it is most needed. Attack of a weakly basic amine is significantly aided by proton removal ($\beta > 0$), whereas the reaction of a strongly basic amine does not require such assistance ($\beta \sim 0$). Conversely, the expulsion of imidazole by the relatively small driving force provided by a weakly basic nucleophile requires complete protonation ($\alpha \sim 1.0$), whereas expulsion driven by a stronger base can occur with only partial proton donation ($\alpha < 1.0$).

(6) D. Oakenfull, K. Salvesen, and W. P. Jencks, unpublished experiments.

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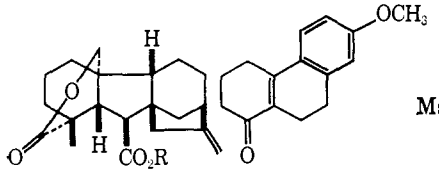
The Stereocontrolled Total Synthesis of *dl*-Gibberellin A_{15}

Sir:

Considerable efforts have long been devoted by many research groups to construct gibberellin molecules and very recently Mori, *et al.*,[1] have succeeded, although in a formal sense, in a total synthesis of some C_{19} gibberellins. In the present communication, we wish to report a stereocontrolled total synthesis of gibberellin A_{15}[2] (**1**) in the racemic form.



1, R = H
2, R = CH_3

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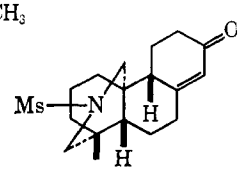

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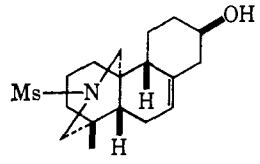
The conjugated ketone **4**, a key intermediate in our previous total synthesis of diterpene alkaloids,[3] prepared from the tricyclic conjugated ketone **3** (24% yield through nine steps), was transformed into a mixture (mp 177–179°) of the enols **5** and **6** (*ca.* 4:1) by dienol acetylation and subsequent $NaBH_4$ reduction.[4] Ozonization, reduction, and successive alkaline treatment of the mixture gave the dihydroxy aldehyde **7**, mp 234–235.5°[5] (34% from **4**) and some amounts of unchanged



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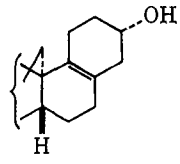

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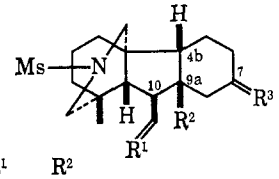
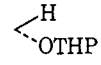
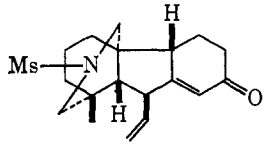


	R^1	R^2	R^3
7,	O	OH	
8,	O	OH	
9,	CH_2	OH	
10,	CH_2	OH	O
12,	CH_2	CN	O
13,	CH_2	CN	
14,	CH_2	CN	
15,	CH_2	CHO	
16,	CH_2	*t*-CH=CH—CHO	
17,	CH_2	*t*-CH=CH—CHO	
18,	CH_2	*t*-CH=CHCH(OAc)$_2$	
19,	O	*t*-CH=CHCH(OAc)$_2$	



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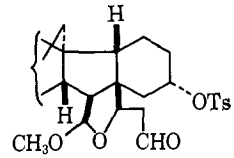

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(1) (a) K. Mori, M. Shinozaki, N. Itaya, T. Ogawa, M. Matsui, and Y. Sumiki, *Tetrahedron Lett.*, 2183 (1968); (b) K. Mori, M. Shinozaki, N. Itaya, M. Matsui, and Y. Sumiki, *Tetrahedron*, 25, 1293 (1969).

(2) (a) B. E. Cross, R. H. B. Galt, and J. R. Hanson, "Regulations Naturels de la Croissance Vegetale," Centre National de la Recherche Scientifique, Paris, 1964, p 265; (b) J. R. Hanson, *Tetrahedron*, 23, 733 (1967).

(3) (a) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, 85, 2342 (1963); 89, 1483 (1967); (b) W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, 86, 929 (1964); 89, 1499 (1967).

(4) *Cf.* B. Belleau and T. F. Gallagher, *ibid.*, 73, 4458 (1951).

(5) (a) All the intermediates show reasonable spectral data and those for which melting points are recorded give satisfactory compositional analyses. (b) The 9aβ and 10β configurations of the newly formed substituents were assigned on the following bases: (i) the ir spectra