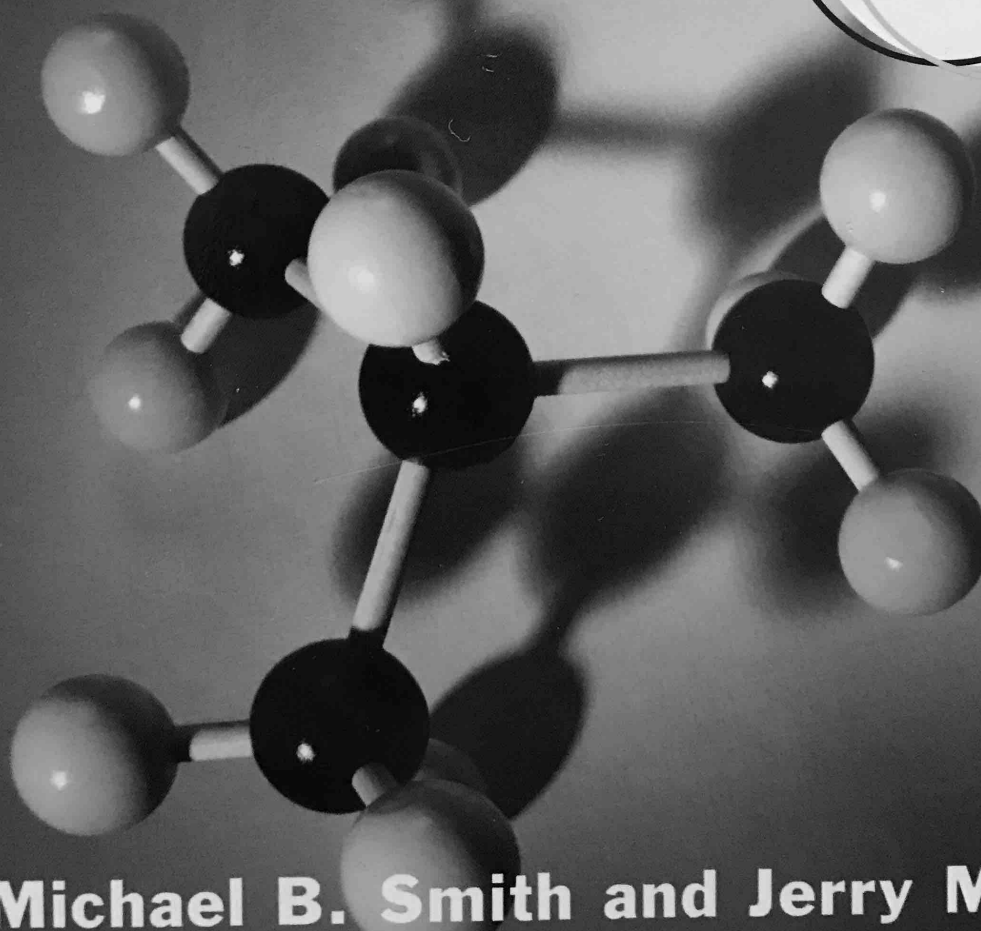


MARCH'S

Advanced Organic Chemistry

Reactions, Mechanisms, and Structure

5th edition



Michael B. Smith and Jerry March

MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS, AND STRUCTURE

FIFTH EDITION

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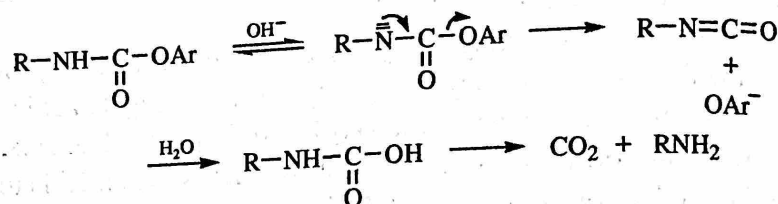
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In the special case of alkaline hydrolysis of N-substituted aryl carbamates, there is another mechanism⁶⁰⁷ involving elimination-addition:⁶⁰⁸



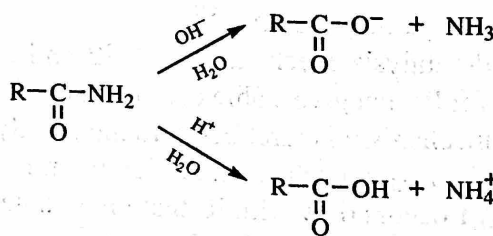
This mechanism does not apply to unsubstituted or N,N-disubstituted aryl carbamates, which hydrolyze by the normal mechanisms. Carboxylic esters substituted in the α position by an electron-withdrawing group (e.g., CN or COOEt) can also hydrolyze by a similar mechanism involving a ketene intermediate.⁶⁰⁹ These elimination-addition mechanisms usually are referred to as E1cB mechanisms, because that is the name given to the elimination portion of the mechanism (p. 1308).

The acid-catalyzed hydrolysis of enol esters ($\text{RCOOCR}'=\text{CR}$) can take place either by the normal $\text{A}_{\text{AC}}2$ mechanism or by a mechanism involving initial protonation on the double-bond carbon, similar to the mechanism for the hydrolysis of enol ethers given in 10-6,⁶¹⁰ depending on reaction conditions.⁶¹¹ In either case, the products are the carboxylic acid RCOOH and the aldehyde or ketone $\text{R}_2''\text{CHCOR}'$.

OS I, 351, 360, 366, 379, 391, 418, 523; II, 1, 5, 53, 93, 194, 214, 258, 299, 416, 422, 474, 531, 549; III, 3, 33, 101, 209, 213, 234, 267, 272, 281, 300, 495, 510, 526, 531, 615, 637, 652, 705, 737, 774, 785, 809 (but see OS V, 1050), 833, 835; IV, 15, 55, 169, 317, 417, 444, 532, 549, 555, 582, 590, 608, 616, 628, 630, 633, 635, 804; V, 8, 445, 509, 687, 762, 887, 985, 1031; VI, 75, 121, 560, 690, 824, 913, 1024; VII, 4, 190, 210, 297, 319, 323, 356, 411; VIII, 43, 141, 219, 247, 258, 263, 298, 486, 516, 527. Ester hydrolyses with concomitant decarboxylation are listed at reaction 12-38.

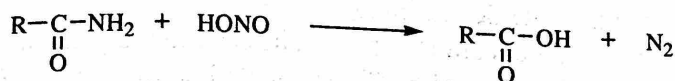
10-11 Hydrolysis of Amides

HYDROXY-DE-AMINATION



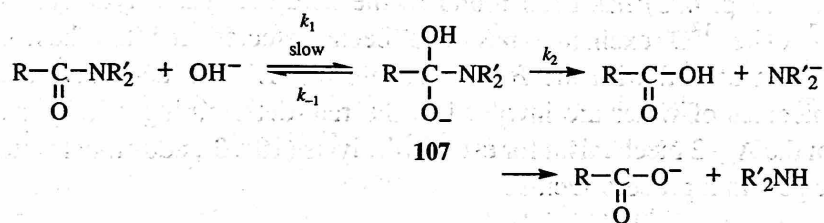
Unsubstituted amides (RCONH_2) can be hydrolyzed with either acidic or basic catalysis, the products being, respectively, the free acid and the ammonium ion or the salt of the acid and ammonia. N-Substituted (RCONHR') and N,N-disubstituted (RCONR_2) amides can be hydrolyzed analogously, with the primary or secondary amine, respectively (or their salts), being obtained instead of ammonia. Lactams, imides, cyclic imides, hydrazides, and so on, also undergo the reaction. Water alone is not sufficient to hydrolyze most amides, since NH_2 is even a poorer leaving group than OR .⁶¹² Prolonged heating is often required, even with acidic or basic

catalysts.⁶¹³ In difficult cases, nitrous acid, NOCl, N₂O₄,⁶¹⁴ or a similar compound can be used (unsubstituted amides only⁶¹⁵).

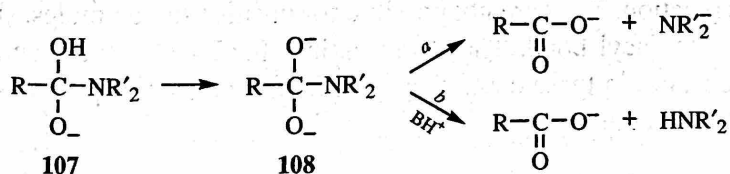


These reactions involve a diazonium ion (see 12-47) and are much faster than ordinary hydrolysis; for benzamide the nitrous acid reaction took place 2.5×10^7 times faster than ordinary hydrolysis.⁶¹⁶ Another procedure for difficult cases involves treatment with aqueous sodium peroxide.⁶¹⁷ In still another method, the amide is treated with water and *t*-BuOK at room temperature.⁶¹⁸ The strong base removes the proton from 107, thus preventing the reaction marked k_{-1} . A kinetic study has been done on the alkaline hydrolyses of *N*-trifluoroacetyl aniline derivatives.⁶¹⁹ Amide hydrolysis can also be catalyzed by nucleophiles (see p. 427).

The same framework of eight possible mechanisms that was discussed for ester hydrolysis can also be applied to amide hydrolysis.⁶²⁰ Both the acid- and base-catalyzed hydrolyses are essentially irreversible, since salts are formed in both cases. For basic catalysis⁶²¹ the mechanism is B_{AC}2.



There is much evidence for this mechanism, similar to that discussed for ester hydrolysis. A MO study on the mechanism of amide hydrolysis is available.⁶²² In certain cases, kinetic studies have shown that the reaction is second order in OH⁻, indicating that 107 can lose a proton to give 108.⁶²³ Depending on the nature



of R', 108 can cleave directly to give the two negative ions (path *a*) or become N-protonated prior to or during the act of cleavage (path *b*), in which case the products are obtained directly and a final proton transfer is not necessary.⁶²⁴ Studies of the effect, on the rate of hydrolysis and on the ratio k_{-1}/k_2 , of substituents on the aromatic rings in a series of amides CH₃CONHAr led to the conclusion that path *a* is taken when Ar contains electron-withdrawing substituents and path *b* when electron-donating groups are present.⁶²⁵ The presence of electron-withdrawing groups helps stabilize the negative charge on the nitrogen, so that NR'₂⁻ can be a leaving group (path *a*). Otherwise, the C—N bond does not cleave until the nitrogen is protonated (either prior to or in the act of cleavage), so that the leaving group, *even in the base-catalyzed reaction*, is not NR'₂⁻ but the conjugate NHR'₂ (path *b*). Though we have

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