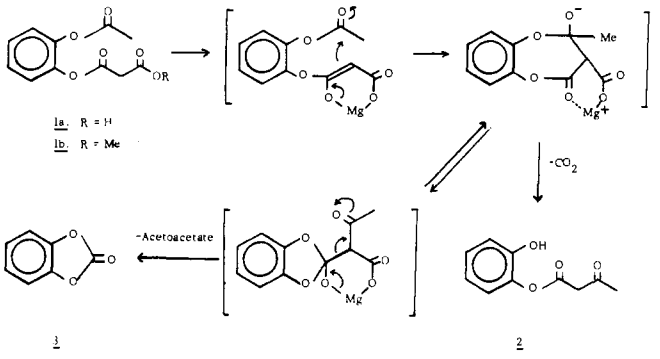
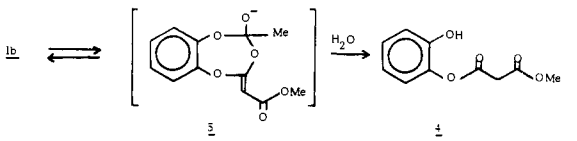
Scheme II



Scheme III



lents of fresh isopropyl magnesium bromide in THF at room temperature for 3 hr, catechol monoacetoacetate (**2**) (30% yield; ir ($CHCl_3$) 3400, 3010, 1770, 1720 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (s, 3 H), 3.75 (s, 2 H), 6.8-7.2 (m, 4 H))[4] and catechol carbonate (**3**) (40% yield; mp 116-118°, lit. mp[6] 120°; ir (KBr) 1850, 1830, 1480 cm^{-1}) were isolated after acidic aqueous work-up. The catechol monoacetoacetate (**2**) was identified by comparison with an authentic sample synthesized from catechol and diketene in refluxing toluene. The NMR spectrum of the crude product mixture revealed that catechol monoacetoacetate (**2**) and catechol carbonate (**3**) were present in a 1/1 ratio as the only products (Scheme II).

Treatment of **1a** with 1 equiv of isopropyl magnesium bromide over a prolonged period at room temperature gave unchanged starting material upon acidification. Reaction of **1a** with 1 equiv of base, followed by heating at refluxing toluene temperature gave the product of simple decarboxylation, catechol diacetate, indicating that the concerted decarboxylative acetyl transfer[3] did not occur. The intramolecular nature of the condensation was suggested by a control experiment in which magnesium monoethyl malonate failed to condense with catechol monoacetate under identical conditions. Bases other than isopropyl magnesium bromide (e.g., sodium hydride, triethylamine, *n*-butyllithium etc.) failed to convert catechol acetate malonate (**1a**) to catechol monoacetoacetate (**2**). Attempts to trap any intermediate before decarboxylation proved futile, suggesting that decarboxylation was occurring very rapidly upon acidic work-up.

When the methyl ester (**1b**) (oil; ir (neat) 1770, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.60 (s, 2 H), 3.78 (s, 3 H), 7.23 (s, 4 H))[4] was similarly treated with isopropyl magnesium bromide, acetyl transfer did not occur. The product mixture contained only the starting material (**1b**) and a hydrolysis product, catechol monomethylmalonate (**4**) (oil; ir (neat) 3420, 1775, 1730 cm^{-1}; NMR ($CDCl_3$) δ 3.6 (s, 2 H), 3.75 (s, 3 H), 6.9-7.2 (m, 4 H))[4] again in a 1/1 ratio. Most likely, the hydrolysis of **1b** is the consequence of a nucleophilic catalysis involving a species such as **5** (Scheme III).[7]

It is noteworthy that in successful acetyl transfer, magnesium chelation is evidently required not for the catalytic decarboxylation but for the control of the C-acetylation over possible O-acetylation. An extension of this scheme to the synthesis of longer fatty acids and polyketides is in progress.[8]

Acknowledgment. We would like to thank the National Science Foundation (Grant GP33505) for the generous support of this work.

References and Notes

(1) F. Lynen, *Biochem. J.*, **102**, 381 (1967); "Chemical Reactivity and Biological ole of Functional Groups in Enzymes", R. M. S. Smellie, Ed., Academic Press, London, 1970, p 1; N. M. Packter, "Biosynthesis of Acetate-derived Compounds", Wiley, London, 1973.
(2) For reviews of other models, see T. Money, *Chem. Rev.*, **70**, 553 (1970); T. M. Harris, C. M. Harris, and K. B. Hindley, *Prog. Chem. Org. Nat. Prod.*, **31**, 217 (1974); A. I. Scott, D. G. Pike, J. J. Ryan, and H. Guilford, *Tetrahedron*, **27**, 3051 (1971), and preceding papers in this series.
(3) The first mechanism (a) involves a concerted, decarboxylative acetyl transfer, and the second possible mechanism (b) involves an intermediate carboxylated species which could be subsequently decarboxylated to give rise to the formation of the enol form of the acetoacetate (see Scheme I).
(4) Satisfactory elemental analyses were obtained for all new compounds.
(5) A. Green, *J. Chem. Soc.*, 500 (1927).
(6) G. Barger, *J. Chem. Soc.*, **93**, 568 (1908).
(7) A. J. Kirby and A. R. Fersht, *Prog. Biorg. Chem.*, **1**, 1 (1971).
(8) Note Added in Proof. An additional control experiment in which resorcinol acetate malonate failed to give resorcinol monoacetoacetate upon treatment with 2 equiv base also supports the *intra*molecular transfer mechanism.

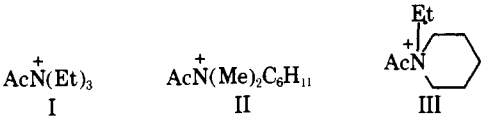
A. Ian Scott,* C. J. Wiesner, S. Yoo, Sung-Kee Chung
Sterling Chemistry Laboratory, Yale University
New Haven, Connecticut 06520
Received March 10, 1975

The N-Protonation Route in the Acid-Catalyzed Hydrolysis of Amides

Sir:

Convincing evidence[1] has been reported in favor of the O-protonation mechanism for acid-catalyzed amide hydrolysis. However, only crude *upper* limits for the proportion of the reaction via the N-protonation route result from these methods. In contrast to the predominant O-protonation route for hydrolysis, denitrosation and deamination of nitrosoamides probably occurs with prior N protonation.[2] There is also evidence that other electrophiles complex with amide nitrogen as in some iodine-amide complexes[3] and some metal catalyzed amide hydrolyses.[4] Moreover, N protonation of a peptide substrate has often been postulated in some proteolytic enzymes[5] including carboxypeptidase A where the X-ray crystallographic evidence is convincing.[6a] Since there is some evidence in favor of N protonation in amide hydrolysis[6b] we are interested in the factors controlling the O or N protonation route, and it is the purpose of this work to provide a reliable estimate of the latter's contribution to the overall acid hydrolysis of *N,N*-dialkylacetamides.

Smith and Yates[1b] mentioned the use of nonprotonic *N*-acylammonium salts as models for N-protonated amides; only *N*-acylpyridinium and -imidazolium species were available as stable moieties but these are not sufficiently similar to the intermediate to give reliable estimates. We present here the kinetic and hydrolytic data for the hydrolysis of *N*-acetyl *N,N,N*-trialkylammonium tetrafluoroborates[7] which are good models.



I II III

The hydrolysis of the salts (see Table I) obeys first-order kinetics[8] and is independent of pH up to neutral pH's but is inhibited at high acidities.

Table I. Rate Constants for Hydrolysis of Substrates[a]

Salt[f]	k_{H_2O}, sec^{-1} [b] ($\times 10^3$)	pK_a (amide-NH^+)[d]	k_{H^+},[c] M^{-1} sec^{-1} (A; $\times 10^9$) (calcd)	k_{H^+},[e] M^{-1} sec^{-1} (B; $\times 10^8$)	A/B	F[g]
I. BF_4^-	2.3	−7.18	0.15	2.9	0.0052	0.52
II. BF_4^-	31	−7.16	2.1	3.8	0.055	0.55
III. BF_4^-	22	−6.93	2.6	81	0.0032	0.32

[a] Ionic strength made up to 1 M with NaCl; 25°. [b] Measured spectrophotometrically: I, 235 nm; II, 235 nm; III, 250 nm. Maximum uncertainty in rate constants is ±5%. [c] Calculated from k_{H_2O}/K_a(amideNH^+). [d] Calculated from the equation in ref 1d; see ref 9. [e] Rate constants are extrapolated from measurements at higher temperatures; rates were followed using an NMR technique. *N,N*-Diethylacetamide, $\Delta H^\ddagger$, 15.1; $\Delta S^\ddagger$, −41.4; *N*-methyl-*N*-cyclohexylacetamide, $\Delta H^\ddagger$, 16.3; $\Delta S^\ddagger$, −30.7; *N*-acetylpiperidine, $\Delta H^\ddagger$, 18.3; $\Delta S^\ddagger$, −32 ($\Delta H^\ddagger$ and $\Delta S^\ddagger$ are in kcal/mol and entropy units per mole, respectively, and the values are for 84.3°). [f] We were unable to entirely remove the amine hydrochloride impurity from the salt; we estimated molarity and hence purity of the stock solutions in acetonitrile by reaction with acetate buffers and allowing the product acetic anhydride to hydrolyze. Purities up to 70% were estimated from the extinction change of the anhydride at 250 nm. [g] This represents the fraction of the reaction passing through the N-protonated intermediate and is derived from A/B by correcting for steric factors (see text).

We may calculate the acid-catalyzed rate constant for the N-protonation path for the secondary amides *N,N*-diethylacetamide, *N*-methyl-*N*-cyclohexylacetamide, and *N*-acetylpiperidine knowing the pK_a of the N-protonated amide[9a] and using the rate constant for hydrolysis of I, II, and III, respectively, as a model for the hydrolysis of the intermediate. The ratio of the value so obtained to the observed acid-catalyzed rate constant (A/B) gives a lower limit to the fraction of the reaction proceeding via N protonation as the prior step. The true fraction is obtained from this ratio after correcting for the steric effect of methyl or ethyl compared with hydrogen; if we assume a Taft delta of unity for the selectivity to E_s (this is a reasonable value since a delta of unity is defined for the sterically similar addition of water to ethyl esters of carboxylic acids in acid hydrolysis)[9b] then replacing hydrogen in tertiary carbon by methyl or ethyl should decrease the reactivity by 1 or 2 logarithmic units, respectively.[9b] By analogy the same effect should be expected when nitrogen is the central atom. The values represented by F in the table are probably *upper* limits for the fraction of reaction passing through the N-protonation path because there is evidence that the steric hindrance is not as pronounced as is to be expected from the delta values: for example 2-methylpropionyl chloride is only fourfold more reactive to water than is pivaloyl chloride.[12]

There will be a difference in solvation between (for example) the N-protonated form of *N*-acetylpiperidine and III. The former will be more strongly solvated, through specific hydrogen bonding to water molecules, because of its NH^+ group. Thus in going from cation to transition state the N-protonated amide should start off lower in energy and tend to react more slowly indicating that the value F may be too high an upper limit. It is difficult to estimate how far below F this upper limit should be: the Bronsted α for solvation by water of NH^+ must be less than unity (which represents complete proton transfer) and a reasonable value seems to be close to 0.2.[14] If we may assume the transition state approximates an N-protonated carbinolamine then a ΔpK_a of about 15 for NH^+ will reduce the ratio F to 0.32×10^{-3} as the upper limit for the fraction of the N-protonation pathway.

The overall selectivity of acid hydrolysis via N-protonation to leaving group pK_a is estimated to be approximately +0.5 being composed of a selectivity of +1.04 for the N-protonation equilibrium[1d] and close to −0.5 for hydrolysis of the intermediate.[13] Since the observed selectivity for acid hydrolysis of substituted anilides is approximately zero[15] (this could be used as an argument in favor of O protonation) then the N-protonation mechanism will predominate for amides of highly basic amines.

References and Notes

(1)(a) A. J. Kresge, P. H. Fitzgerald, and Y. Chiang, *J. Am. Chem. Soc.*, **96**, 4698 (1974); (b) C. R. Smith and K. Yates, *Can. J. Chem.*, **50**, 771 (1972); (c) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000, 2007, 2009 (1957); (d) A. R. Fersht, *J. Am. Chem. Soc.*, **93**, 3504 (1971); (e) R. S. Molday and R. G. Kallen, *ibid.*, **94**, 6739 (1972); (f) R. B. Martin, *J. Chem. Soc., Chem. Commun.*, 793 (1972); (g) R. B. Martin and W. C. Hutton, *J. Am. Chem. Soc.*, **94**, 4752 (1972); (h) A. C. Hopkinson and I. G. Csizmadia, *Can. J. Chem.*, **51**, 1432 (1973); (i) H. Benderly and K. Rosenheck, *J. Chem. Soc., Chem. Commun.*, 179 (1972).

(2) B. C. Challis and S. P. Jones, *J. Chem. Soc., Perkin Trans. 2*, 153 (1975).

(3) R. S. Drago and D. Bafus, *J. Phys. Chem.*, **65**, 1066 (1961).

(4) R. P. Houghton and R. R. Puttner, *Chem. Commun.*, 1270 (1970).

(5) L. Parker and J. H. Wang, *J. Biol. Chem.*, **243**, 3729 (1968).

(6)(a) J. A. Hartsuck and W. N. Lipscomb in "The Enzymes", Vol. 3, 3rd ed, P. D. Boyer, Ed., Academic Press, New York, N.Y., p 1; (b) M. Liler, "Reaction Mechanisms in Sulphuric Acid", Academic Press, New York, N.Y., 1971, p 106

(7) J. V. Paukstelis and Moon-geu Kim, *J. Org. Chem.*, **39**, 1503 (1974).

(8) The hydrolysis may be followed by uv absorption (Table I) or with a pH–stat; in the latter case the amount of acid released follows a logarithmic plot (vs. time) consisting of two linear phases: a high rate constant identical with that from the uv work and a smaller one equal to the rate constant for acetic anhydride hydrolysis under the same conditions. In acetate buffers the absorption at 250 nm increased and then decayed at the rate expected for acetic anhydride hydrolysis suggesting that in the pH–stat experiments acetic anhydride is formed by capture of the initial acetate product by the acetylammonium salt (present in relatively high concentrations ~10 mM).

(9)(a) Estimates of pK_a for the N-protonated amide depend on acid catalyzed proton exchange[1e,10,11] and on models of equilibria in thermodynamic cycles.[1d] The good agreement between the results gives us confidence in the equation: $pK_a = -18.6 + 1.04pK_{a\,(R_2NH)}$[1d] where R_2NH is the free amine; (b) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13.

(10)(a) I. M. Klotz and B. H. Frank, *J. Am. Chem. Soc.*, **87**, 2721 (1965); (b) A. Berger, A. Lowenstein, and S. Meiboom, *ibid.*, **81**, 62 (1959).

(11) C. L. Perrin, *J. Am. Chem. Soc.*, **96**, 5628, 5631 (1974).

(12) R. F. Hudson, *Chimia*, **15**, 394 (1961).

(13) A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432 (1970).

(14) R. W. Taft, D. Gurka, L. Joris, P. v. R. Schleyer, and J. W. Rakshys, *J. Am. Chem. Soc.*, **91**, 4801 (1969).

(15) V. F. Mandyuk and N. P. Lushina, *Ukr. Khim. Zh.*, **32**, 607 (1966).

Andrew Williams

University Chemical Laboratories
Canterbury, Kent, England

Received July 10, 1975

Aromatic Radical Anions in Neat Solvents. Crown Complex Ion-Pair Formation

Sir:

Reports[1,2] of radical anion formation in neat benzene and toluene using crown ethers and alkali metals prompt us to describe our experimental results with 18-crown-6. We hope our direct observation of the role played by ion-pair formation in the case of mesitylene and toluene will assist other workers. To our knowledge this is also the first report of the preparation of the mesitylene radical anion. The observed reactivity, in contrast to the very weak electron affinity of mesitylene in other solvents and in the absence of crown ether complex, may be due to the stabilization of the anion radical by ion-pair formation.

Samples are prepared under high vacuum conditions by bringing a solution of 18-crown-6 in benzene, toluene, or mesitylene, into contact with an alkali metal mirror. The reaction begins quickly and is complete after a few hours at −20°C.