$$F = \frac{k_2 - k_0(1 - e^{-k_2 t})}{k_2 - k_0} = \frac{k_2 - k_0(\text{mol fraction of amine from III})}{k_2 - k_0} \quad (16)$$

if k_2 is known from independent measurement of the rate of lactonization of III. For the hydrolysis of I in bicarbonate buffer at pH 9, k_2 was accurately known (Table II). In other experiments, corrections were based on single point determinations of the yield of amine from samples of III which had been allowed to undergo lactonization for a time period equal to that used in the complete hydrolysis of I. Observed and corrected yields of benzylamine are listed in Table I.

Values of K_{app} and ΔA_{max} were calculated by means of a computer fit of the data to the two-parameter rectangular hyperbola.[26]

Acknowledgment. Support of this research by a grant from the National Science Foundation is gratefully acknowledged.

Medium and Temperature Dependence of Acid-Catalyzed Hydrolysis of N-Methylated Methylbenzimidates and Benzoylimidazole. An Investigation into the Mechanism of Amide Hydrolysis

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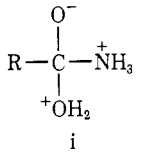
Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario. *Received April 24, 1972*

Abstract: The kinetics of hydrolysis of methylbenzimidate, *N,O*-dimethylbenzimidatium fluoroborate, and *N,N,O*-trimethylbenzimidatium fluoroborate have been studied in 1–65% aqueous sulfuric acid over the temperature range 25–85°. The hydrolysis of benzoylimidazole was studied in 10–75% sulfuric acid over the temperature range 15–65°. The benzimidates yielded esters as primary hydrolysis products in dilute acid but gave amides as products in more concentrated acids, indicating different rate-determining steps in dilute and concentrated acids. The order of reactivity with successive N-methylation was primary > secondary > tertiary and there were monotonic decreases in both the enthalpy and entropy of activation with successive N-methylation. By comparing rate constants, activation parameters, product studies and ^{18}O exchange results for the N-methylated methylbenzimidates and the corresponding N-methylated benzamides, it is concluded that none or not all of the benzamides hydrolyze in acid solution *via* the accepted tetrahedral intermediate mechanism (involving an O-protonated amide) as do the benzimidates. Inspection of data for benzoylimidazole (as a model for an N-protonated amide) does not contradict this conclusion.

Despite the importance of acid-catalyzed hydrolysis of amides, the mechanism of this reaction is still uncertain. A number of mechanisms can be envisaged, but the two most reasonable mechanistic pathways are outlined in Scheme I. These can be designated as A_OT2 (acid-catalyzed, bimolecular, O-protonated cation, tetrahedral intermediate mechanism) and A_ND2 (acid-catalyzed, bimolecular, N-protonated cation, direct displacement mechanism), respectively.[1] Various authors have regarded one or another of these mechanisms as being correct, with the majority favoring the A_OT2 mechanism. However, there is no evidence whatever to rule out either; thus the correct mechanism is not established.

It was shown previously[2] that changes in first-order rate constants and enthalpies of activation for the acid-catalyzed hydrolysis of benzamide are not monotonic with successive N-methylation. It was clear that these changes were either the result of a mechanistic change with successive N-methylation or some unexplained phenomenon of a unique mechanism of amide hydrolysis. Edward and Meacock[3] have proposed that methylbenzimidate would be a good chemical model for benzamide hydrolyzing *via* the O-protonated form (A_OT2 mechanism) since imidates in general react through tetrahedral intermediates.[3,4] In this paper, the effect of successive N-methylation of methylbenzimidate on hydrolysis rate constants and activation parameters will be examined. If the benzamides and benzimidates react *via* similar tetrahedral intermediates, the reaction parameters for these two types of substrate should exhibit similar changes with successive N-methylation. The substrates to be compared are listed in Chart I. The amides are represented in their predominant O-protonated form[5] and the benzimidates in their protonated or cationic forms.

(1) One other mechanism is possible which closely resembles the A_ND2 mechanism. In this process water attacks the N-protonated species to give a discrete tetrahedral intermediate (A_NT2). However, because of the highly dipolar nature of such an intermediate (i), it is



i

considered to represent a less reasonable mechanistic pathway, although the possible intermediates involved in these two alternative mechanisms would be very difficult to distinguish experimentally.

(2) C. R. Smith and K. Yates, *J. Amer. Chem. Soc.*, **93**, 6578 (1971).

(3) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2009 (1957).

(4) R. K. Chaturvedi and G. L. Schmir, *J. Amer. Chem. Soc.*, **90**, 4413 (1968); R. H. DeWolfe and R. B. Augustine, *J. Org. Chem.*, 30, 699 (1965).

(5) C. R. Smith and K. Yates, *Can. J. Chem.*, **50**, 771 (1972); A. R. Katritzky and R. A. Y. Jones, *Chem. Ind. (London)*, 722 (1961); R. J. Gillespie and T. Birchall, *Can. J. Chem.*, **41**, 148, 2642 (1963); G. A. Olah and P. J. Szilagyi, *J. Amer. Chem. Soc.*, **91**, 2949 (1969).

Table I. Products of Benzimidate Hydrolysis

Substrate	% acid	Time, hr	Temp, °C	% material recovered	% products[a] Methyl benzoate	Amide	Benzoic acid	Starting material
Methylbenzimidate	5	48	25		100	0	0	0
	43	1	85	88	35	0	51	14
	65	16	85	85	0	5	40	55
N,O-Dimethyl-benzimidatium fluoroborate	5	48	25		100	0	0	0
	43	2	85	102	35[b]	8[b]	51	8
	62	51	85	96	0	27	45	28
	65	65	85	106	0	33	37	30
N,N,O-Trimethyl-benzimidatium fluoroborate	5	48	25		100	0	0	0
	65	118	85	93	0	25	36	39

[a] Values normalized to 100% yields. Estimated errors are about ±5% of values listed. [b] Relative amounts of amide and ester determination by nmr.

Scheme I

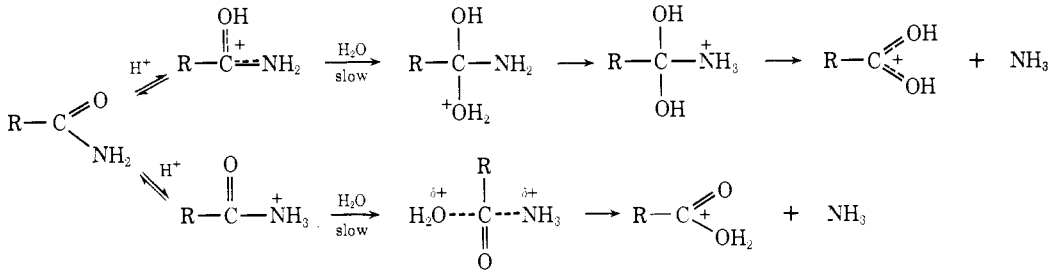
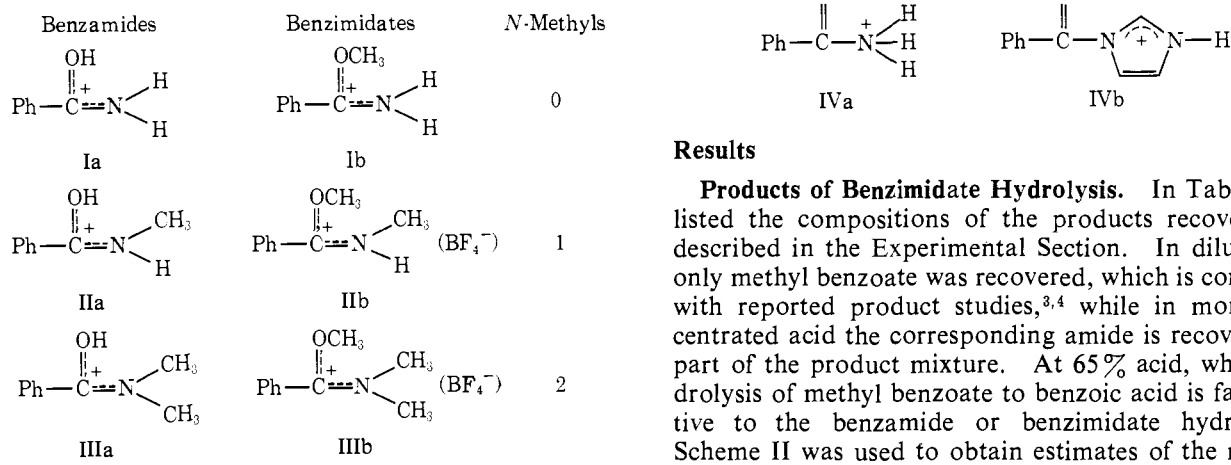


Chart I



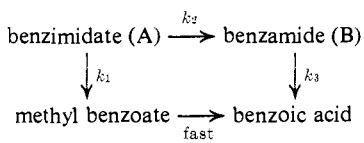
Proposed model substrates for an N-protonated amide are acyltrialkylammonium salts[6] and acylpyridinium salts.[7] However, the benzoyl derivatives[8] are thermally unstable at room temperature. The best model available in the benzoyl series was benzoylimidazole (IVb). This has been studied by Marburg and Jencks[9] in HCl but no rate profile in sulfuric acid has been determined. In comparing the N-protonated amide IVa with IVb, it should be recognized that the charge in IVb is delocalized onto both nitrogens while in IVa it is localized. Therefore IVb is expected to be much less reactive than IVa and to represent only a lower limit for the reactivity of an N-protonated amide (by the A_NP2 mechanism).

(6) C. A. Bunton, C. O'Connor, and T. A. Turney, *Chem. Ind. (London)*, 1835 (1967).
(7) A. R. Fersht, *J. Amer. Chem. Soc.*, **93**, 3504 (1971).
(8) A. K. Sheinkman, S. L. Portnova, Yu. N. Skeinker, and A. N. Kost, *Dokl. Akad. Nauk SSSR*, **157**, 1416 (1964); *Dokl. Chem.*, 817 (1964); R. Gompper and P. Altreuther, *Z. Anal. Chem.*, **170**, 205 (1959).
(9) S. Marburg and W. P. Jencks, *J. Amer. Chem. Soc.*, 84, 232 (1962).

Results

Products of Benzimidate Hydrolysis. In Table I are listed the compositions of the products recovered as described in the Experimental Section. In dilute acid only methyl benzoate was recovered, which is consistent with reported product studies,[3,4] while in more concentrated acid the corresponding amide is recovered as part of the product mixture. At 65% acid, where hydrolysis of methyl benzoate to benzoic acid is fast relative to the benzamide or benzimidate hydrolysis[10] Scheme II was used to obtain estimates of the rates of

Scheme II



formation of ester, k_1, and the corresponding benzamide, k_2, from the benzimidates. Analysis of this scheme yields the equations

$$k_{obsd} = (-2.303/t) \log ([A]_t/[A]_0) = k_1 + k_2$$

$$k_2 = \frac{[B]_t(k_3 - k_{obsd})}{[A]_0(e^{-k_{obsd}t} - e^{k_3 t})}$$

Values of k_3 were measured by independently following the rate of hydrolysis of the appropriate benzamide. The rate constants, with errors calculated from the

(10) Compare data in ref 2 and C. A. Lane, M. F. Cheung, and G. Dorsey, *J. Amer. Chem. Soc.*, **90**, 6492 (1968).

Table II. Rates of Ester and Amide Formation for Benzimidate Hydrolysis in Sulfuric Acid at 85°

Substrate	10^4k_{obsd}, min^{-1}	10^4k_3,[c] min^{-1}	10^4k_1,[a,d] min	10^4k_2,[b,d] min	k_2/k_{obsd}	% acid
Methylbenzimidate	6.23	9.58	5.12 ± 2.28	1.11 ± 0.26	0.18 ± 0.08	65
N,O-Dimethylbenzimidatium fluoroborate	3.06	1.49	1.05 ± 0.70	2.01 ± 0.44	0.65 ± 0.18	65
N,O-Dimethylbenzimidatium fluoroborate	4.14	1.93	1.94 ± 0.84	2.20 ± 0.48	0.53 ± 0.14	62
N,N,O-Trimethylbenzimidatium fluoroborate	1.33	3.78	−0.57 ± 0.56	1.90 ± 0.46	1.43 ± 0.48	65

[a] Rate of formation of ester. [b] Rate of formation of amide. [c] Values measured by sampling technique. [d] Errors quoted are two standard deviations (95% confidence level) as obtained from formulas derived from the propagation of errors formula assuming a standard deviation of 10% in the normalized product compositions (Table I).

Table III. Oxygen Exchange during Acid Hydrolysis at 85°

Benzamide			*N*-Methylbenzamide			*N,N*-Dimethylbenzamide		
Time, hr[a]	% ^{18}O[b]	σ[c]	Time, hr[a]	% ^{18}O[b]	σ[c]	Time, hr[a]	% ^{18}O[b]	σ[c]
0	2.64	0.03	0	2.83	0.18	0	3.44	0.03
123	2.79	0.06	290	2.87	0.05	290	3.45	0.06
218	2.90	0.04	797	2.92	0.05	622	3.48	0.05
340	2.88	0.04	1178	2.94	0.04	797	3.52	0.02

[a] These times correspond to 0, 1, 2, and 3 half-lives, respectively, for amide hydrolysis in 80% H_2SO_4. [b] Determined by comparing peaks in mass spectrum corresponding to PhC=^{16}O and PhC=^{18}O. [c] Standard deviation.

propagation of errors formula,[11] assuming a 10% error in the per cent compositions, are listed in Table II. These rates show an increase in the relative rate of amide formation (k_2/k_{obsd}) with successive N-methylation.

^{18}O Exchange in Benzamides. Benzamide and *N*-methyl- and *N,N*-dimethylbenzamide, enriched with ^{18}O, were hydrolyzed in 80% sulfuric acid (*i.e.*, where benzimidates give predominantly or exclusively benzamide by a process analogous to ^{18}O exchange in amides). Unreacted amide was recovered at various times and analyzed for ^{18}O content. The results presented in Table III show clearly that no significant ^{18}O exchange takes place under these conditions for any of the three amides. The lower limit of $k_{hydrolysis}/2k_{exchange}$ can be estimated to be of the order of 10.[12]

Rates of Hydrolysis. Methylbenzimidate and *N,N*-dimethylbenzimidatium fluoroborate gave excellent first-order plots by the *in situ* and sampling kinetic techniques described in the Experimental Section. However, *N,O*-dimethylbenzimidate gave curved first-order kinetics by the *in situ* technique. Nonlinear first-order kinetic plots for N-methylated imidates have been observed previously to be due to syn–anti isomerization occurring simultaneously with hydrolysis.[13] However, attempts to detect two isomers by vpc and nmr failed. By following the rate of product formation by the recovery technique described in the Experimental Section, good first-order kinetics were in fact obtained for *N,O*-dimethylbenzimidate as well, indicating that if two isomers exist, they react at nearly identical rates. The rate constant obtained in this manner at 85° (2.30×10^{-2} min^{-1}) agrees reasonably well with the value determined for IIb by the *in situ* technique (2.13×10^{-2} min^{-1}). The fluoroborate salt (IIb) gave excellent linear first-order plots by the *in situ* technique and therefore was used to determine the rate of hydrolysis of the *N*-methyl derivative.

It was established for Ib that varying the anion from bisulfate to fluoroborate had no detectable effect on the rate constant. In Table IV are listed rate constants for Ib, IIb, and IIIb over the range of acidity and temperature investigated for each substrate. These values have errors of ±2% as determined by the reproducibility of the values from duplicate runs. The rate constants for benzoylimidazole are presented in Table V. Good first-order kinetics were obtained for this substrate by both the *in situ* and sampling techniques.

Activation Parameters. Activation parameters listed in Table VI were calculated at constant water activity as described previously.[2] For benzoylimidazole the calculations at constant water activity could not be made directly but were obtained from values calculated at constant per cent acid as described by Smith.[14] These are listed in Table VII. The errors quoted are derived from the least-squares expressions for the standard deviations of the slope and intercept[15] of plots of log k_p/T *vs.* $1/T$.

Discussion

Product and ^{18}O-Exchange Studies. It can be seen from the data in Table I that benzimidate hydrolyses show a change in product from ester plus amine formation to amide plus alcohol formation as acid strength is increased (Scheme III). From the rate constants in Table II, k_6 becomes comparable with or greater than k_7 at about 65% acid for Ib and IIb, and for IIIb (R = R_1 = R_2 = CH_3) amide is the only significant primary

(11) H. P. Young, "Statistical Treatment of Experimental Data," McGraw-Hill, New York, N. Y., 1962, p 98.

(12) This is a conservative estimate based on the accuracy of the mass spectral data, as indicated by the standard deviations in Table III. Any rate of exchange approaching one twentieth of the hydrolysis rate would easily have been detectable.

(13) W. P. Jencks, personal communication.

(14) C. R. Smith, Ph.D. Thesis, University of Toronto, 1971.

(15) W. J. Youden, "Statistical Methods for Chemists," Wiley, New York, N. Y., 1951, pp 42, 43.

Table IV. Rate Constants for the Rate of Hydrolysis of Benzimidates

A. *N*-Methylated Benzimidates

% acid	$k_p \times 10^4$, min^{-1} [a] 85.15°	65.12°	54.94°	25.01°
	Methylbenzimidate			
12.46	6860	1470		30.3
18.70	4790	995		19.2
23.62	3360	709		12.4
27.28	2610	505		8.68
32.55	1630	316		4.63
36.63	1030[a]	192		2.65
36.63	1050[b]			
43.02	485	79.5	28.2	0.935
47.61	226	36.5	12.5	0.380
51.71	118	17.0	5.52	0.157
54.85	62.5	8.68	2.90	0.0737
57.78	32.9	4.40	1.51	0.0337
60.28	18.7	2.37	0.798	0.0167
62.63	10.3	1.25	0.423	0.00777
	N,O-Dimethylbenzimidatium Fluoroborate			
	85.15°		70.40°	54.94°
12.46	4450			
18.70	2980			
23.62	1920			
27.28	1470			
32.55	885			
36.63	521			
43.02	213			
47.61	78.3			
51.86	43.5			
52.08			10.8	2.28
55.11	26.3			1.27
54.88			6.13	
57.90	16.4		3.28	0.638
60.40	9.52		1.93	0.363
62.66	5.97			
62.71			1.20	0.205
	N,N,O-Trimethylbenzimidatium Fluoroborate			
	85.15°		70.40°	54.90°
12.46	1240			
18.71	724			
23.62	451			
27.28	282			
32.55	110			
36.63	65.7			
43.27	14.6			
51.86	5.65			
52.08			1.25	0.238
55.11	3.32		0.777	0.132
57.90	2.00		0.495	0.0738
60.40	1.48		0.312	0.0520
62.66	1.10			
62.71			0.243	0.0387

B. Benzimidates in 12.5% Acid

Temp, °C	k_p, min^{-1} [c] Methylbenzimidate	*N,O*-Dimethylbenzimidatium fluoroborate	*N,N,O*-Trimethylbenzimidatium fluoroborate
85.15	0.686	0.445	0.124
64.90		0.118	
64.80			0.0340
64.12	0.147		
44.66	0.0230	0.0199	0.00690
25.01	0.00303	0.00358	0.00132

[a] Determined on Cary 16 spectrophotometer (sampling technique). [b] Determined on Bausch and Lomb 505 spectrophotometer (*in situ* technique). [c] Rate constants were previously defined[2] for amide hydrolysis based on the concentration of substrate in the protonated form, *i.e.*, $k_p = k_{obsd}([S] + [SH^+])/[SH^+]$. For strongly basic substrates such as the benzimidates and benzoylimidazole, which are fully ionized at all acidities used, k_p is equivalent to k_{obsd}.

Table V. Rate of Hydrolysis of Benzoylimidazole in H_2SO_4 at 25°

% acid	k_p, min^{-1} 15.54°	25.0°	34.53°	44.92°	54.31°	64.23°
12.46		1.26				
18.71		0.861				
23.62		0.630				
27.28		0.478				
32.55	0.138	0.312	0.638	1.22		
36.63		0.212				
43.02		0.118				
47.61		0.0824				
51.71		0.0560				
54.85		0.0428				
57.78		0.0330				
62.66		0.0229	0.0547	0.141	0.303	0.645
67.88		0.0223				
70.36		0.0160				
72.82		0.0138				
75.36		0.0141				
77.77		0.0132				

Table VI. Activation Parameters for Benzimidate Hydrolysis[a]

$-\log a_w$	$\Delta H^{\ddagger}$, kcal/mol	σ[b]	$\Delta S^{\ddagger}$, eu	σ[b]
	Methylbenzimidate			
0.05	18.78	0.19	−16.13	0.59
0.1	18.95	0.40	−16.97	1.22
0.15	19.16	0.27	−17.56	0.82
0.20	19.35	0.37	−18.11	1.12
0.25	19.36	0.26	−19.09	0.79
0.30	19.48	0.28	−19.73	0.88
0.35	19.70	0.26	−19.98	0.81
0.40	19.96	0.22	−20.09	0.68
0.45	20.10	0.15	−20.51	0.45
0.50	20.15	0.13	−21.19	0.39
0.55	20.21	0.07	−21.82	0.23
0.60	20.33	0.04	−22.21	0.12
0.65	20.42	0.06	−22.64	0.19
0.70	20.60	0.17	−22.82	0.52
	N,O-Dimethylbenzimidatium Fluoroborate			
0.025	16.39	0.17	−22.92	0.53
0.425	20.02	1.05	−22.1	3.06
0.45	20.11	0.91	−22.25	2.66
0.50	20.30	0.88	−22.39	2.58
0.55	20.69	0.91	−22.02	2.65
0.60	20.88	0.88	−22.12	2.58
0.65	21.27	0.91	−21.61	2.66
0.70	21.73	0.44	−20.86	1.31
0.75	22.17	0.75	−20.11	2.20
	N,N,O-Trimethylbenzimidatium Fluoroborate			
0.025	15.3	0.20	−28.4	0.60
0.45	21.39	0.31	−22.86	0.90
0.50	22.04	0.00	−21.64	0.01
0.55	22.66	0.23	−20.42	0.68
0.60	23.1	0.69	−19.72	2.01
0.65	23.19	0.21	−19.88	0.62
0.70	23.43	0.46	−19.61	1.34
0.75	23.43	0.15	−19.9	0.46

[a] Calculated at constant water activity for each temperature range. [b] Standard deviation.

hydrolysis product (*i.e.*, $k_6 \gg k_7$). From ^{18}O-exchange studies of ethyl benzoate hydrolysis,[16] an alcohol molecule leaves the tetrahedral intermediate about five times as fast as a water molecule.[17] If this were the

(16) M. L. Bender, R. D Ginger, and J. P. Unik, *J. Amer. Chem. Soc.*, 80, 1044 (1958); see also ref 18.

(17) Similar conclusions can be drawn from the rates of hydrolysis and exchange of other esters in acid solution.[18] A referee has suggested that the relative rates with which water and methanol leave these tetrahedral intermediates could change with medium and hence affect the present conclusions at different acidities. However, the values observed for $k_{hydrolysis}/k_{exchange}$ for alkyl acetate hydrolysis are remarkably insensitive to the medium from 20 to 70% H_2SO_4.[18]

(18) K. Yates, *Accounts Chem. Res.*, 4, 136 (1971).

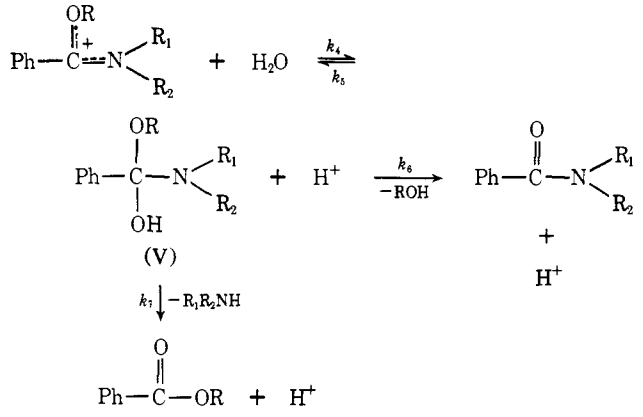
Table VII. Activation Parameters for Benzoylimidazole Hydrolysis

% acid	ΔH, kcal/mol	σ^a	$-\Delta S$, eu	σ^a
32.55	12.59	0.43	25.6	1.4
62.77	16.5	0.13	18.9	0.43

$-\text{Log } a_w$	ΔH,[b] kcal/mol	$-\Delta S^b$
0.15	12.5	27.1
0.91	15.8	21.1

[a] Standard deviation. [b] Calculated from values at constant % acid by the method described by Smith.[14]

Scheme III



case ($k_6 \simeq 5k_5$) for the analogous benzimidate intermediates, the intermediate V would revert back to starting materials at a significant rate ($k_5 > k_7$) in moderate to concentrated acid, and attack of water (k_4) would no longer be solely rate determining, at least for the N-methylated derivatives. This is in contrast to the situation in dilute acid where only amine leaves the intermediate ($k_7 \gg k_6$) for all three imidates.

If the corresponding benzamides hydrolyze by the analogous A_OT2 mechanism, involving similar intermediates (V, R = H), then in dilute acid they would not be expected to show ^{18}O exchange. This has been shown to be the case.[6,19] However, in more concentrated acid (65% or greater) they should exhibit significant ^{18}O exchange. Available data[6,19] did not extend to this acidity; hence studies were carried out in 80% acid where the possibility of ^{18}O exchange would be expected to be even greater. The data in Table III show that no detectable exchange takes place for any of the three amides.

In the case of IIIb (R = R_1 = R_2 = CH_3), the products and rate analysis suggest that alcohol leaves intermediate V at least 20 times as fast as amine ($k_6 = 20k_7$) in 65% acid. It is reasonable that the relative leaving group abilities of alcohol and water would be similar in V to those in the analogous ester hydrolysis intermediates (*i.e.*, $k_6 \simeq 5k_5$). Thus for the amide hydrolysis intermediate (V, R = H) k_5 would be about four times as large as k_7 and hence ^{18}O exchange would be expected to be *faster* than hydrolysis. Because only half of the water molecules lost from V (R = H) would lead to exchange, the predicted $k_{hydrolysis}/k_{exchange}$ ratio would be about 0.5. However, the *lower limit* of this ratio for IIIb based on the ^{18}O exchange results in Table III is 26. Clearly the two results are inconsistent. A similar analysis for IIb leads to a similar inconsistency, particularly when it is considered that exchange should increase in going from 65 to 85% acid. Thus it is extremely doubtful that either *N,N*-dimethyl- or *N*-methylbenzamide could be hydrolyzing by way of tetrahedral intermediate analogous to V and yet not show any detectable ^{18}O exchange under these experimental conditions.[20] No conclusion can be made about benzamide itself.

Relative Reactivities. Because of the change in the rate-determining step observed for the benzimidates, direct rate comparisons are restricted to the dilute acid region where both substrate types undergo rate-determining attack by water. In Table VIII are listed the rates at log $a_w = -0.1$ (% $H_2SO_4 \simeq 30$) for the benzamides and benzimidates at 85°. The benzimidates exhibit a monotonic decrease in rate with successive N-methylation while the benzamides show an irregular order.[21] The relative rates imply that an anomaly occurs for the N-alkylated substrates which exhibit a relative rate factor of ~40 compared with values of ~4 for the other two sets of substrates. Again it seems very doubtful whether all three amides can be hydrolyzing by a similar mechanism (A_OT2) to the three imidates.

Table VIII. Relative Rates of Benzamide and Benzimidate Hydrolysis at 84°

N-Methyls	k_p, min^{-1} (log $a_w = -0.1$) Benzimidate	Benzamide	Rel rate
0	0.227	0.0575	3.95
1	0.126	0.00331	38.1
2	0.0227	0.006	3.75

In contrast to the similar overall reactivities of the benzimidates and benzamides, a comparison of the data in Tables IV and V at 25° shows a rate factor of $\sim 10^3$ at log a_w = 0.1 between methylbenzimidate and benzoylimidazole which should represent a lower limit for the relative reactivity of an N- *vs.* an O-protonated amide. Therefore, the ratio of equilibrium concentrations of N-protonated to O-protonated amides can be no greater than 10^{-3} to yield the observed rates of hydrolysis, a concentration not easily detected.[22]

Activation Parameters. The activation parameters for imidate hydrolysis listed in Table VI are typical of bimolecular hydrolyses, which normally exhibit large positive enthalpies of activation and large negative entropies of activation. In contrast with the analogous benzamides,[1] $\Delta H^{\neq}$ does not remain constant for each substrate over the range of acidity investigated. These

(19) M. L. Bender and R. D. Ginger, *J. Amer. Chem. Soc.*, 77, 348 (1955); M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

(20) It is possible that no exchange is observed because equilibration of the oxygens in the intermediate is slow compared to its decomposition. We thank a referee for pointing this out. However, rapid proton transfers between the two oxygens can evidently take place rapidly enough in the analogous imidate species before the intermediate decomposes, and at comparable acidities, as judged by their predominant formation of amides as products at high acidities.

(21) This irregular order (primary > tertiary > secondary) is found for benzamide hydrolysis for a wide range of temperature and acidity.[2] A similar irregular order has been reported for the analogous acetamide hydrolyses by P. D. Bolton, *Aust. J. Chem.*, **19**, 1013 (1966).

(22) Recent estimates of the ratio of N-protonated to O-protonated forms of amides are of the order of 10^{-3} to 10^{-7};[7] H. Benderly and K. Rosenheck, *Chem. Commun.*, 179 (1972).

facts are consistent with the benzamides exhibiting no mechanistic change over the whole acid range, while the benzimidates clearly do exhibit a change in rate determining step at higher acidities. Because of the uncertainties in the mechanism of hydrolysis of acylimidazoles,[9] the medium dependence of $\Delta H^{\pm}$ calculated for benzoylimidazole can not be interpreted at this time. In Table IX are the activation parameters for both series at log $a_w = -0.025$.

Table IX. Activation Parameters for the Benzamides and Benzimidates at Log $a_w = -0.025$

	Benzamides		Benzimidates	
Methyls	$\Delta H^{\pm}$, kcal/mol	$-\Delta S^{\pm}$, eu	$\Delta H^{\pm}$, kcal/mol	$-\Delta S^{\pm}$, eu
0	20.3	14.4		
1	21.2	17.5	18.8	16.1
2	18.4	24.2	16.4	22.9
3			15.3	28.4

The changes in entropy of activation for the benzimidates fit the explanation proposed[1] to explain the observed changes in $\Delta S^{\pm}$ for the benzamides. In fact the entropies are very similar for the substrates with one (IIa and Ib) and two methyl groups (IIIa and IIb). This gives considerable support to the proposed argument; however, as previously stated,[2] $\Delta S^{\pm}$ would not be very sensitive to the various mechanistic possibilities (*i.e.*, tetrahedral-like transition state or displacement-type transition state).

The observed changes in $\Delta H^{\pm}$ with methyl substitution are in sharp contrast to the benzamide results and the six values cannot be explained by assuming that all six substrates are hydrolyzing *via* a common mechanism. The benzimidates exhibit a monotonic decrease in $\Delta H^{\pm}$ with successive N-methylation. This change is opposite to that expected for the inductive effect of a methyl group and is attributed to the decrease in the extent of solvation of the protonated form with successive N-methylation. As solvation is lost the positive charge is localized more on the protonated imidate functional group and dispersed less to solvent, which facilitates the attack of the nucleophile, water. However, at 85°, the unfavorable entropy change with methyl substitution overbalances this favorable enthalpy change and the rate of hydrolysis decreases with successive N-methylation. Since the benzimidates are all reacting *via* the tetrahedral intermediate mechanism, it is clear that there are no anomalous variations to be expected from this mechanistic pathway in either rates or activation parameters with successive N-methylation. This is contrary to what is observed for the benzamide series.[2] The activation parameters for benzoylimidazole reveal nothing that eliminates the N-protonated form as a possible reactive species. The entropy is sufficiently negative for there to be no doubt that it is a bimolecular reaction. This is also implied by the eventual decrease in the observed rate constant with increasing acidity (*i.e.*, as the concentration of the water is diminished).

Conclusions

The complete lack of parallelism between the various reaction parameters for acid catalyzed benzimidate and benzamide hydrolysis casts serious doubt on the frequently accepted hypothesis that amide hydrolysis generally involves the O-protonated form and formation of a tetrahedral intermediate (*i.e.*, an A_OT2 type mechanism analogous to the $A_{Ac}2$ mechanism of ester hydrolysis).

Two possibilities seem reasonable. Firstly, primary, secondary, and tertiary amides all react *via* the minor N-protonated form (A_ND2), since N-methylation could then affect both the extent of N-protonation relative to O-protonation and the reactivity of this form, yielding an irregular order of reactivity. Also no ^{18}O exchange would be expected from this mechanism under any experimental conditions. Alternatively only primary amides such as benzamides could react *via* the O-protonated form by way of the A_OT2 mechanism, whereas *N*-methyl- and *N,N*-dimethylbenzamides could be reacting *via* the N-protonated form and the A_ND2 mechanism. This could be explained by the steric difficulty in forming tetrahedral intermediates with increased N-substitution and concomitant release of steric crowding achieved in a direct displacement mechanism. The high reactivity of benzoylimidazole, and other acylammonium cations, demonstrates that the A_ND2 process could support the observed rates if the N-protonated form were a very minor species relative to the predominant O-protonated form.

Experimental Section

Analyses were performed by A. G. Gygli, 329 St. George St., Toronto 181, Ontario.

Substrates. Methylbenzimidate hydrochloride was prepared according to the method of Pinner.[23] The hydrochloride salt was converted to the neutral compound by placing the salt in ether and washing with 1 *M* Na_2CO_3 in a separatory funnel. The ether was removed and the resultant oil was distilled, bp 63° (1.8 mm). *Anal.* Calcd for C_8H_9ON: C, 71.07; H, 6.72; N, 10.37. Found: C, 71.10; H, 6.89; N, 10.42.

General Alkylation Procedure. The Meerwein reagent, trimethyl fluoroborate (VI), was prepared by the standard procedure.[24] Equimolar quantities of the alkylating reagent and substrate were mixed in methylene chloride (0.1 mol per 25 ml solvent) and were allowed to stir 16 hr at room temperature. The slurry (VI is insoluble in methylene chloride) turns to a homogeneous solution indicating that reaction has occurred. Ether was added to precipitate the fluoroborate salt. *N,O*-Dimethylbenzimidatium fluoroborate (II) was prepared by the O-methylation of *N*-methylbenzamide by the general procedure. The salt was recrystallized from methylene chloride, mp 126.5–127.5°. *Anal.* Calcd for $C_9H_{12}ONBF_4$: C, 45.59; H, 5.10; N, 5.91. Found: C, 45.12; H, 5.30; N, 6.00.

N,O-Dimethylbenzimidate was prepared by decomposing the salt with 1 *M* Na_2CO_3 as described for methylbenzimidate and was purified by distillation, bp 51.0–51.1° (0.7 mm) (lit.[25] 91–94° (13 mm)). *Anal.* Calcd for $C_9H_{11}ON$: C, 72.44; H, 7.44; N, 9.40. Found: C, 72.64; H, 7.58; N, 9.60.

N,N,O-Trimethylbenzimidatium fluoroborate (III) was prepared by the O-alkylation of *N,N*-dimethylbenzamide according to the general alkylation procedure and was recrystallized from a 50:50 mixture of methylene chloride and 1,2-dichloroethane, mp 107.5–108.5°. *Anal.* Calcd for $C_{10}H_{14}ONBF_4$: C, 46.82; H, 5.62; N, 5.58. Found: C, 47.23; H, 5.61; N, 5.84.

Benzoylimidazole (IV) was prepared by the method of Gerngoss.[26] The oil was purified by distillation, bp 92–93° (0.5 mm). *Anal.* Calcd for $C_{10}H_8ON_2$: C, 69.74; H, 4.69; N, 16.27. Found: C, 69.88; H, 4.71; N, 15.97.

^{18}O-Labeled Amides. Benzoyl chloride was prepared by the method of Bender[19] using water with 3.84% abundance of ^{18}O

(23) A. Pinner, *Chem. Ber.*, **16**, 352 (1883).
(24) H. Meerwein, *Org. Syn.*, **46**, 120 (1966).
(25) H. Paul, A. Weise, and R. Dettmer, *Chem. Ber.*, **98**, 1450 (1965).
(26) O. Gerngoss, *ibid.*, **46**, 1909 (1913).

(Yeda Research and Development Co., Rehovoth, Israel). Benzamide-^{18}O was prepared as described by Bender, mp 127–128.5°. *N*-Methylbenzamide-^{18}O was prepared by adding benzoyl-^{18}O chloride dropwise to a 40% aqueous solution of *N*-methylamine using 3 equiv of amine to 1 equiv of acid chloride, mp 82–83°. *N,N*-Dimethylbenzamide-^{18}O was prepared by adding benzoyl-^{18}O chloride to a solution of dimethylamine in methylene chloride (3 equiv of amine:1 equiv of acid chloride). The product was purified by distillation at 83.0–83.8° (28 mm).

Determination of Products of Benzimidate Hydrolysis. In 5% sulfuric acid, the substrates were completely hydrolyzed by allowing the solution to stand at room temperature for 48 hr. The product was recovered by extraction with methylene chloride. The ir spectrum of the oil obtained by removing the methylene chloride was shown to be identical with that of methyl benzoate for Ib, IIb, and IIIb.

In more concentrated acids, 1 g of the substrate was dissolved in 5 ml of sulfuric acid and heated at 85° for at least 1 half-life and the sample diluted to yield approximately 20% acid. The products of hydrolysis were recovered by three extractions with methylene chloride for IIb and IIIb and with ethyl acetate for Ib. The benzoic acid was removed from the organic layer by extracting with 1 *M* $NaHCO_3$ and the recovered benzoic acid was identified by ir and weighed. The organic layer was removed and the remaining products weighed and identified by ir and nmr.

Starting material was recovered by making the 20% acid neutral and extracting with methylene chloride. In the case of IIIb, it was hydrolyzed completely to benzoic acid, recovered as benzoic acid and weighed.

Kinetic Methods. The sampling technique used for runs with half-lives longer than 30 min was described previously,[2] as were the preparation and standardization of the sulfuric acids. The *in situ* technique, used for the faster runs, employed a Bausch and Lomb Spectronic 505 equipped with a Microcord auxiliary recorder and a thermostated cell block with control to ±0.05°. Temperatures were standardized against a calibrated thermometer (National Bureau of Standards, Washington) and stem corrected where necessary. The spectral change was monitored on the auxiliary recorder. Runs were initiated by injecting 10 ml of a stock solution of substrate into sulfuric acid that had been preequilibrated to reaction temperature in the cell block and stirred in the cell with a small temperature equilibrated electrically driven glass propellor. This initiation took approximately 5 sec with negligible heat loss. Infinity readings were taken after at least 10 half-lives and were stable to at least 20 half-lives. The wavelengths and substrate concentrations used are listed in Table X. To ensure that only hydrolyses of benzimidate to primary products were being studied and further hydrolysis of methyl benzoate or amide was not contributing to the observed rate, the indicated isosbestic points were used. Above 55% acid, methylbenzimidate hydrolysis gave only a small spectral change at the isosbestic point for methyl benzoate and benzoic acid. However, at 52% acid methyl benzoate is hydrolyzing so much faster than the benzimidates that rates determined at the isosbestic point and 255 mμ gave identical rate constants. Therefore for I, λ 255 mμ was used in acids more concentrated than 52%.

Rate of Product Formation for *N,O*-Dimethylbenzimidate. *N,O*-Dimethylbenzimidate (0.18 g) was added with stirring to 43% sulfuric acid solution (150 ml) which had been preequilibrated to 85°. Samples (10 ml) were withdrawn at regular intervals and quenched in ice water. The samples were diluted with cold water and extracted four times with chloroform. The volume of chloroform was made up to 50 ml and the absorbance recorded at 275.5 mμ (the isosbestic point for methyl benzoate and benzoic acid in chloroform) and at 310 mμ (where neither product absorbs). A residual absorbance due to light scattering by water suspended in the chloroform was removed by use of the expression

$$Ab^* = Ab_{275.5} - 1.1Ab_{310}$$

The rate constant was obtained by a plot of log $(Ab^*_t - Ab^*_\alpha)$ *vs.* *t*, where Ab^*_α was measured after 10 half-lives.

Table X. Substrate Concentration and Wavelength for Kinetic Measurements of Benzimidate Hydrolysis

Acid	Substrate molarity	λ, mμ	Isosbestic point
	Methylbenzimidate		
12.5	$0.5–2.5 \times 10^{-4}$	251.5	Methyl benzoate to benzoic acid
23.6		250.25	*a*
32.6		249.5	*a*
43.0		248.0	*a*
47.6		243.0	*a*
51.7		242.5	*a*
51.7–63		255	
	N,O-Dimethylbenzimidatium Fluoroborate		
12.5–47.6	$0.5–2.5 \times 10^{-4}$	*b*	Methyl benzoate to benzoic acid
52.0		215.1	*N*-Methylbenzamide to benzoic acid
55.1		215.0	*a*
57.9–62.7		214.8	*a*
	N,N,O-Trimethylbenzimidatium Fluoroborate		
12.5–43.3	$0.5–2.5 \times 10^{-4}$	*b*	Methyl benzoate to benzoic acid
52.0		219.1	*N,N*-Dimethylbenzamide to benzoic acid
55.1		219.2	*a*
57.9		219.3	*a*
60.4		219.5	*a*
62.7		219.6	*a*
	Benzoylimidazole		
12.5–78	$0.9–3.0 \times 10^{-4}$	255	

[a] As above. [b] As for methylbenzimidate.

^{18}O Exchange Studies. The amides were hydrolyzed in 85% sulfuric acid at 85° and unreacted amide recovered at appropriate times by extraction after the solution had been made neutral with NaOH, taking care not to let the solution become hot or basic. Ethyl acetate was used to extract benzamide and methylene chloride was used to extract *N*-methyl- and *N,N*-dimethylbenzamide. The recovered amides were purified by sublimation and the mass spectrum was analyzed at mass peaks 105 and 107 corresponding to ^{16}O and ^{18}O benzoyl peaks on an AEI Model Ms902 mass spectrometer.

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