Steric and Electronic Effects in the Hydrolysis of N-Acylimidazoles and N-Acylimidazolium Ions

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The rates of hydrolysis of a series of N-acylimidazoles have been measured in 0.1 *M* HCl at 30°. Increased branching at the α-carbon of the acyl group produces small increases in rate, while branching at the β-carbon results in decreased rates. The relative rate ratios parallel closely those found previously in the hydroxide ion and imidazole catalyzed hydrolysis of these compounds. The rate increases found for the compounds with branching at the α-carbon are due to more favorable values of ΔH^* than would be expected. Branching at the β-carbon produces a large unfavorable effect on ΔH^*. A further similarity in the hydrolysis of the N-acylimidazoles and N-acylimidazolium ions relates to susceptibility to electronic effects; the ρ value for hydroxide ion catalyzed hydrolysis of a series of substituted N-benzoylimidazoles was found to be +1.4. The relative rate ratios for the hydrolysis of the N-acylimidazolium ions are insensitive to changes in solvent composition, being approximately the same in 75% dioxane–water, 50% dioxane–water, and water. Thus, it is probable that the same factor(s) is primarily responsible for the anomalous steric effects found for the hydrolysis reactions in both acid and base, and this factor is likely independent of solvation effects, the most probable explanation being relief of strain in a transition state lying close to products.

The hydrolysis of N-acylimidazoles has received much attention.[1-7] In a previous study[1] it was found that in the general base, general acid, and hydroxide ion catalyzed reactions, steric effects due to branching in the acyl group are anomalous. Increased branching at the α-carbon does not result in an observed steric retardation in rate but actually produces a small rate increase. Branching at the β-carbon does result in a rate decrease but to a smaller extent than found in nucleophilic catalysis of ester hydrolysis. Increased branching at the α-carbon of the acyl group does, however, result in large rate decreases in the aminolysis of N-acylimidazoles in tetrahydrofuran as the solvent.[7] It was suggested[1] that in the general base catalyzed reaction, and presumably also in the hydroxide ion catalyzed reaction, the transition state lies close to products. If a large amount of bond breaking has occurred then steric strain might be relieved upon entering the transition state for hydrolysis of the branched compounds. It is also possible that water structured about the alkyl groups might play a large role in the hydrolytic process and account for the observed steric effects.[1] To obtain further information concerning these effects the hydrolysis of the series of N-acylimidazolium ions has been studied, and activation parameters have been obtained for these reactions.

Experimental Section

Materials.—The imidazole employed was from Eastman Kodak Co. (White Label). Dioxane was purified according to the method of Fieser[8] and stored frozen. Isovaleryl chloride was obtained from Matheson Coleman and Bell. Deuterium oxide (99.8%) was obtained from Bio-Rad Laboratories.

Dioxane solutions were prepared by mixing given volumes of dioxane and water. A desired concentration of HCl in these solutions was obtained by bubbling in the required weight of anhydrous HCl.

A 0.1 *M* solution of DCl in deuterium oxide was prepared by bubbling into the solvent the desired weight of anhydrous HCl. Using the glass electrode correction formula of Fife and Bruice, pD was found to be 0.95.

The N-acylimidazoles were the same as previously described.[1] The isovaleryl derivative was added to the series; it is a liquid boiling at 71–73° (0.5 mm), $n^{24.2}$D 1.4839.

Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.11; H, 8.28; N, 18.20.

The series of substituted N-benzoylimidazoles was prepared by the method of Caplow and Jencks.[10] The physical constants of the products matched closely the values reported by these workers. N-Benzoylimidazole had bp 104–105° (0.25 mm), lit.[11] mp 19–20°.

Kinetic Measurements.—The kinetics of the hydrolysis of the N-acylimidazoles were studied in aqueous 0.1 *M* HCl and 0.19 *M* HCl in 50% and 75% dioxane–water mixtures (v/v). The rates in the acid solutions were measured spectrophotometrically with a Beckman DU spectrophotometer, equipped with a Gilford Model 2000 recording attachment, by following the decrease in absorption at 245 mμ. The material was added, with vigorous stirring, to the thermostated cuvette by means of a microspatula. The rates were generally followed to 75% completion. Infinity points were taken at roughly 10 half-lives.

Pseudo-first-order rate constants were calculated by means of a Honeywell 800 computer using a program designed to carry out multiple regression and correlation analysis. The output of interest consisted of the regression coefficient (rate constant) of $\ln (OD_i - OD_\infty)/(OD_t - OD_\infty)$ *vs.* time, the standard error of the regression coefficient, the intercept value of the log function *vs.* time, and the correlation coefficient. The latter generally had a value between 0.9990 and 0.9999. If the correlation coefficient was below 0.98, the computed value of the rate constant was rejected and determined from a plot of the above log function *vs.* time. Spot checks showed that the values obtained from the computer agreed well with those calculated by hand.

Constant temperature was maintained during the kinetic runs by circulating water from a Haake Model F constant-temperature circulating bath around the cell compartment of the spectrophotometer. The temperature in the 4° run with N-trimethylacetylimidazole was obtained by circulating a 20% alcohol solution through a copper coil immersed in an ice–salt mixture and then around the cell compartment. The temperature of the cell compartment in this run was determined by means of a temperature probe supplied with the Gilford instrument. The temperature was controlled to ±0.1° in the runs above 10° and ±0.5° for the one run at 4°.

The rates of alkaline hydrolysis of the N-benzoylimidazoles were measured titrimetrically with a Radiometer TTT1 Autotitrator and Radiometer Titrigraph. A Metrohm EA 115-X electrode was employed. The procedure and equipment were the same as previously described.[12] The rates were followed to completion, and the pseudo-first-order rate constants were obtained

(1) T. H. Fife, *J. Am. Chem. Soc.*, **87**, 4597 (1965).
(2) W. P. Jencks and J. Carriuolo, *J. Biol. Chem.*, **234**, 1272, 1280 (1959).
(3) S. Marburg and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 232 (1962).
(4) R. Wolfenden and W. P. Jencks, *ibid.*, **83**, 4390 (1961).
(5) R. B. Martin, *ibid.*, **84**, 4130 (1962).
(6) C. A. Bunton, *J. Chem. Soc.*, 6045 (1963).
(7) H. A. Staab, *Ber.*, **89**, 1927, 2088 (1956).
(8) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.
(9) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).
(10) M. Caplow and W. P. Jencks, *Biochemistry*, **1**, 883 (1962).
(11) O. Gerngross, *Ber.*, **46**, 1908 (1913).
(12) T. H. Fife, *J. Am. Chem. Soc.*, **87**, 271 (1965).

by the method of Guggenheim.[13] Identical rate constants were obtained when the initial concentration of substrate was varied over a 2–3-fold range. Rate measurements were made at several pH values with each compound with the exception of N-(*p*-nitrobenzoyl)imidazole which could not be studied conveniently above pH 8.6 at 30° owing to the rapidity of its rate of hydrolysis. The observed rate constants were directly proportional to the hydroxide ion concentration in the pH range studied titrimetrically. The second-order rate constants (k_{OH}) were calculated from $k_{OH} = k_{obsd}a_H/K_w$. The value of K_w at 30° was obtained from the International Critical Tables.[14]

Results

The kinetic results are presented in Tables I–IV. Table I lists the observed rate constants at each temperature for the hydrolysis of the series of N-acylimidazoles in 0.1 *M* HCl where the amide is completely protonated.[2,3] The rates were measured in duplicate or triplicate at each temperature with an average deviation of 2–3% in the rate constants with the exception of those for N-trimethylacetylimidazole which had an average deviation of 6%. The relative rate ratios at 30° are approximately the same as found previously[1] for the general base,[15] general acid, and hydroxide ion catalyzed reactions of these compounds, except that the value for the trimethylacetyl derivative is slightly larger. Increased branching at the α-carbon of the acyl group does not result in observed steric retardation of the rate but actually produces small rate increases. Thus, both N-trimethylacetylimidazole and N-isobutyrylimidazole hydrolyze faster than does N-propionylimidazole. Branching at the β-carbon does result in rate decreases, and in the case of N-triethylacetylimidazole a very slow rate is obtained. Also reported in Table I are the observed rate constants measured in D_2O ($k_H/k_D \geqslant 2.26$).

TABLE I

RATE CONSTANTS FOR THE HYDROLYSIS OF N-ACYLIMIDAZOLES IN 0.1 *M* HCl AT VARIOUS TEMPERATURES AND IN 0.1 *M* DCl AT 30°

N-Acyl group	Temp, °C	k_{obsd}, min^{-1} [a]	k_{rel}	k_{obsd} min^{-1} [b]	k_H/k_D
Acetyl	49.0	11.6			
	39.3	6.57			
	30.0	4.08	0.90		2.50[c]
	20.6	2.19			
Propionyl	39.4	7.79			
	30.0	4.54	1.00	1.83	2.48
	20.6	2.70			
Isobutyryl	39.4	12.0			
	30.0	7.57	1.67	2.78	2.72
	20.6	4.71			
Trimethylacetyl	30.0	31.6	6.96	12.6	2.50
	26.8	28.7			
	20.4	20.8			
	14.0	13.4			
	13.4	13.9			
	12.1	12.3			
	4.0	8.0			
Butyryl	39.4	4.65			
	30.0	2.74	0.60	1.10	2.49
	20.5	1.57			
Isovaleryl	49.4	2.43			
	39.7	1.42			
	30.0	0.814	0.18		
	20.0	0.394			
3,3-Dimethylbutyryl	48.1	0.325			
	39.4	0.197			
	30.0	0.118	0.026	0.0417	2.83
	20.7	0.0627			
Triethylacetyl	49.0	0.0391			
	39.6	0.0211			
	30.0	0.0101	0.0022	0.00446	2.26
	21.1	0.00535			

[a] 0.1 *M* HCl in H_2O. [b] 0.1 *M* HCl in D_2O. [c] Reference 2, 25°.

TABLE II

ACTIVATION PARAMETERS FOR THE HYDROLYSIS OF N-ACYLIMIDAZOLES IN 0.1 *M* HCl AT 30°

Acyl group	ΔH^*, kcal/mole	ΔS^*, eu[a]
Trimethylacetyl	8.6	−31.4
Isobutyryl	8.7	−34.3
Propionyl	9.9	−31.3
Acetyl	10.4	−29.8
Butyryl	9.8	−32.3
Isovaleryl	11.0	−30.7
3,3-Dimethylbutyryl	10.7	−35.8
Triethylacetyl	12.9	−33.3

[a] Values of ΔS^* were calculated at 30° with the rate constants having the units sec^{-1}.

TABLE III

RATE CONSTANTS FOR THE HYDROLYSIS OF N-ACYLIMIDAZOLES IN 0.19 *M* HCl IN 50% DIOXANE–WATER AND 75% DIOXANE–WATER (V/V) AT 30°

N-Acyl group	50% dioxane-H_2O k_{obsd}, min^{-1}	50% dioxane-H_2O k_{rel}	75% dioxane-H_2O k_{obsd}, min^{-1}	75% dioxane-H_2O k_{rel}
Propionyl	1.71	1.00	0.748	1.00
Isobutyryl	3.02	1.77	1.27	1.70
Trimethylacetyl	16.6	9.71	7.40	9.89
Butyryl	1.07	0.63	0.454	0.61
Isovaleryl	0.259	0.15	0.133	0.18
3,3-Dimethylbutyryl	0.0470	0.027	0.0255	0.034
Triethylacetyl	0.00415	0.0024	0.00291	0.0039

TABLE IV

RATES OF ALKALINE HYDROLYSIS OF N-BENZOYLIMIDAZOLES IN WATER AT 30° AND μ = 1.0 *M* WITH KCl

Compound	k_{OH}[a] l. mole^{-1} min^{-1}
N-(*p*-Methoxybenzoyl)imidazole	8,100
N-(*p*-Methylbenzoyl)imidazole	12,900
N-Benzoylimidazole	21,000
N-(*p*-Chlorobenzoyl)imidazole	41,000
N-(*p*-Nitrobenzoyl)imidazole	251,000

[a] $k_{OH} = k_{obsd}a_H/K_w$.

Table II lists the activation parameters for hydrolysis of the N-acylimidazoles in 0.1 *M* HCl. It can be seen that increased branching at the α-carbon of the acyl group results in progressively lower values of ΔH^*, accounting for the fact that steric retardation of the rate is not observed with these compounds. Branching at the β-carbon results in more positive values of ΔH^* and with the 3,3-dimethylbutyryl and triethylacetyl derivatives in more negative ΔS^* values. A small compensation in the activation parameters may exist for a series composed of N-isobutyrylimidazolium ion and those derivatives having straight chain acyl groups. A plot of ΔH^* *vs.* ΔS^* for the hydrolysis of these compounds (Figure 1) is linear with a slope of 375° K. The temperature at which the relative rate ratios were obtained (30°) is therefore 72° below the apparent isokinetic temperature.[16] The points on this plot for those compounds having very bulky acyl groups, trimethylacetyl, 3,3-dimethylbutyryl, and triethylacetyl, show large deviations from the isokinetic line.

(13) E. A. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(14) "International Critical Tables," Vol. VI, E. W. Washburn Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1929, p 152.

(15) The values of k_{Im} reported in ref 1 are actually $k_{Im} - k_{ImH}$. Since k_{ImH} is small in comparison with k_{Im} the differences are slight and the relative rate ratios are essentially unaffected.

(16) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).

In Table III are reported rate constants for hydrolysis of the N-acylimidazoles in 0.19 M HCl in 50% dioxane–water and 75% dioxane–water (v/v). The relative rate ratios are quite similar in these solvents to those obtained in water. Changing the aqueous content of the solvent and the solvent dielectric constant, therefore, affects the rates of hydrolysis of all the compounds in the same manner which would indicate that solvation factors or water structuring about the alkyl groups is probably not responsible for the observed relative rate ratios.

In Table IV are given values of k_{OH} for hydrolysis of a series of substituted N-benzoylimidazoles. In Figure 2 the logarithms of these values are plotted *vs.* σ, the Hammett substituent constant.[17] The value of ρ obtained from the slope of this plot is +1.4, showing that the bond-making process (attack of the nucleophilic hydroxide ion) is quite important in the transition state.

Discussion

It was previously suggested[1] that for hydrolysis reactions of the neutral species the observed steric effects, which are highly unusual for bimolecular reactions, are the result of compensating effects: (a) a normal rate-retarding effect due to the increased difficulty of approach to the carbonyl by a nucleophile as branching in the acyl group is increased, and (b) a rate-accelerating effect produced by increased branching. If the rate-accelerating effect was due to water structuring effects by the alkyl groups[18] then it might reasonably be expected that the ΔS^* values would become more positive as branching was increased since more water would be restricted in the ground state, resulting in a smaller difference between the number of water molecules involved in the ground states and in the transition states. However, in 0.1 M HCl ΔH^* was found to decrease with increased branching at the α-carbon and increase with branching at the β-carbon. Changes in ΔS^* are smaller and more complex, but it would appear that ΔS^* generally tends to become more unfavorable as steric bulk in the acyl group is increased. It is apparent that branching results in faster rates of hydrolysis than would normally be expected because of relatively favorable ΔH^* values.

The results of studies in 0.19 M HCl in the solvents 50% dioxane–water and 75% dioxane–water, showing that the relative rate ratios are approximately the same in these solvents as in water, indicate further that specific solvation effects are probably not causing the accelerating effect. In dioxane–water mixtures it is likely that the nonpolar alkyl groups would be solvated by dioxane to a large extent. If water structuring about the alkyl group was an important factor in these reactions then compounds with large bulky acyl groups should be affected more by changing solvent composition than those with comparatively small acyl groups, but this is not observed. Water orientation and availability for reaction, however, are certainly important factors and will be discussed further in a succeeding paper. The results also suggest that the transition state has approximately the same polarity for each compound since otherwise the relative rate ratios should depend on the dielectric constant of the solvent.

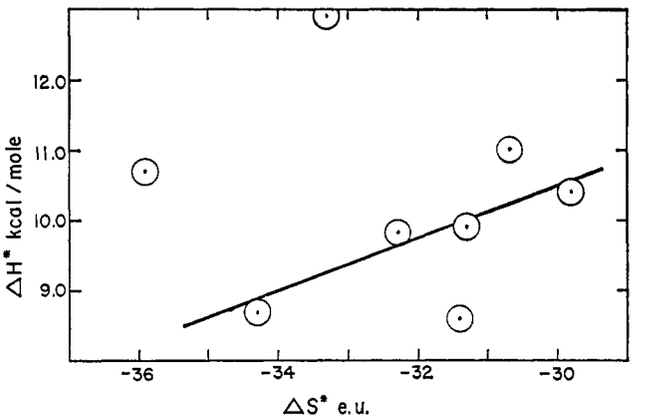


Figure 1.—A plot of ΔH^* *vs.* ΔS^* for the hydrolysis of the series of N-acylimidazoles in 0.1 M HCl.

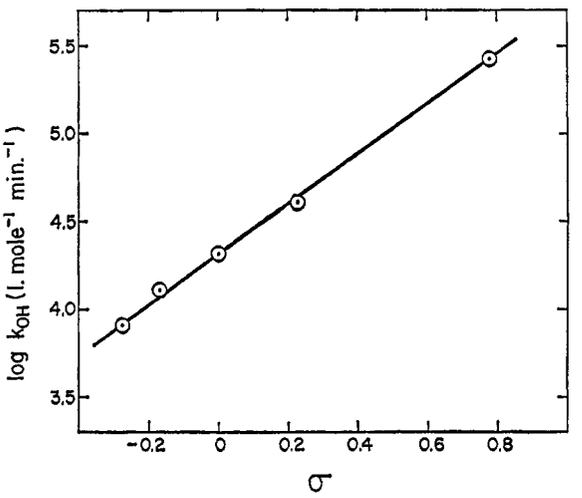


Figure 2.—A plot of log k_{OH} *vs.* σ, the Hammett substituent constant, for the hydrolysis of a series of *para*-substituted N-benzoylimidazoles in water at 30°.

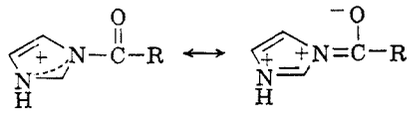
A further piece of evidence indicating that similar factors are influencing the hydrolysis of the N-acylimidazolium ions and the hydroxide ion catalyzed hydrolysis of the neutral species is the susceptibility to electronic effects. The hydrolysis of a series of substituted N-benzoylimidazoles in 0.1 M HCl was previously found to give a ρ value of +1.7[10] when the logarithms of the rate constants were plotted *vs.* σ, the Hammett substituent constant. In the present study a ρ value of +1.4 has been found for alkaline hydrolysis of the same series of compounds. The similarity of the two values indicates that attack at the carbonyl (bond making) is an important feature of both reactions.

Staab[7] has suggested that the faster rate of hydrolysis in conductivity water for N-acylimidazoles with branching at the α-carbon of the acyl group is due to twisting of the carbonyl group out of coplanarity with the imidazole ring, thereby reducing resonance interaction and resulting in a less stable molecule. Marburg and Jencks[8] have postulated the same effect to explain the similar rates of hydrolysis of N-acetylimidazole and N-benzoylimidazole in 0.1 M acid. Assuming that the kinetically important species has a ring nitrogen pro-

(17) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

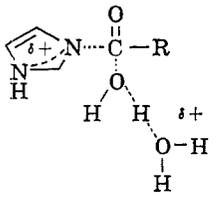
(18) H. S. Frank and M. W. Evans, *J. Chem. Phys.*, **13**, 507 (1945); I. M. Klotz, *Science*, **128**, 815 (1958); G. Némethy and H. A. Scheraga, *J. Chem. Phys.*, **36**, 3382, 3401 (1962).

tonated to afford a good leaving group,[19] resonance between the ring and the carbonyl would necessitate the importance of resonance structures having more than one positive charge residing on the imidazole ring which should not be favorable in comparison to the resonance structures that can be written for the neutral species. Thus, if inhibition of resonance was



the principle cause of the observed abnormal order of reactivity in reactions of the neutral species then it would be expected that a more nearly normal order would be obtained in the hydrolysis of N-acylimidazolium ions which, of course, is not the case. Also, ground-state effects such as steric inhibition of resonance between the ring and the carbonyl would not explain why a normal steric order is obtained in the aminolysis reaction with diethylamine.[7] Thus, there is apparently a feature of the hydrolysis transition state which allows the accelerating effect due to acyl group branching to become important.

A transition state for the hydrolysis of N-acylimidazolium ions in which the carbon–nitrogen bond is breaking in concert with nucleophilic attack by a water



molecule, so that relief of strain would occur, is consistent with all of the data presently available. This mechanism is exactly analogous to that proposed previously[1] for the imidazole-catalyzed hydrolysis of the neutral species.

All of the compounds hydrolyze more slowly in acidic D_2O, k_H/k_D being equal to or greater than 2.26 in each case. These values are in accord with proton transfer in the rate-determining step[20] as shown, although neither the actual number of water molecules involved nor their mode of action can be specified with certainty. Jencks and Carriuolo[21] have previously suggested that in the hydrolysis of N-acetylimidazolium ion more than one molecule of water is involved, arriving at this conclusion on the basis of the D_2O solvent isotope effect, large negative ΔS^*, and salt and acid effects.

A concerted type of mechanism, such as shown, in which the leaving group departs as the nucleophile attacks, would not involve a kinetically significant tetrahedral intermediate in which the oxygen atoms can become equivalent and, therefore, it would be predicted that O^{18} exchange into the amide carbonyl would not occur when the reaction was run in water enriched with O^{18}. This is consistent with the results obtained by Bunton[6] in a study of the hydrolysis of N-acetylimidazolium ion where little O^{18} exchange was found.

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(19) This assumption is supported by the finding of Wolfenden and Jencks[4] that the hydrolysis of 1-acetyl-3-methylimidazolium ion serves as a model for the hydrolysis of N-acetylimidazolium ion.

(20) F. A. Long, *Ann. N. Y. Acad. Sci.*, **84**, 596 (1960).

(21) W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, **83**, 1743 (1961).

Benzo[c]quinolizinium Salts *via* Intramolecular Cylization[1,2]

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cis-2′-Chloro-2-stilbazoles, obtained by irradiation of the *trans* form with ultraviolet light, cyclize intramolecularly at suitable temperatures affording benzo[*c*]quinolizinium salts. A direct formation of benzo[*c*]quinolizinium salts is achieved by treating *trans*-2′-chloro-2-stilbazoles with iodine at high temperatures. Certain 5-substituted benzo[*c*]quinolizinium salts are obtained directly in the initial condensation between an α-substituted picoline and 2-chlorobenzaldehyde.

Earlier work carried out in this laboratory has afforded convenient methods for the synthesis of the benzo[*a*]-[3–5] (phenanthridizinium) and the benzo[*b*]-quinolizinium[6–7] (acridizinium) ions. A convenient method has now been found for the synthesis of the hitherto difficulty accessible[8–9] benzo[*c*]quinolizinium ion III.

It seemed logical to expect that the benzo[*c*]quinolizinium system might be prepared by the intramolecular quaternization of a *cis*-2′-chloro-2-stilbazole. For the initial attempt it was decided to prepare *cis*-2′-chloro-4′-nitro-2-stilbazole (II, $R_4 = NO_2$; X = Cl) in which the chlorine atom is activated by a *p*-nitro group. *trans*-2′-Chloro-4′-nitro-2-stilbazole (Ib) was

(1) This work was described in a preliminary communication by A. Fozard and C. K. Bradsher, *Chem. Commun.*, 288 (1965).

(2) This research was supported by a grant (CA-05509) from the National Cancer Institute of the National Institutes of Health.

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