7: n = 1,   R = C$_{12}$H$_{25}$, R' = H

8: n = 1,   R = R' = C$_{12}$H$_{25}$

9: n = 2,   R = C$_{12}$H$_{25}$, R' = H

10: n = 2,   R = R' = C$_{12}$H$_{25}$

Compound **5** is the second amphiphile ever discovered to form CPBMs in water. Apparently, the structure of the coordination sphere of the CPBMs of **5** matches the geometry of the assembly of the hydrophobic tails. Many molecular functions can be expected from the CPBMs as exemplified by the hydrolytic cleavage of chymotrypsin by the Co(III)-CPBM of **3** within a few minutes at pH 7 and 4 °C.[19] In this respect, characterization of additional functions of CPBMs can be undertaken with both **3** and **5**.

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Theoretical Studies on the Base-Catalyzed Deprotonation of 4-Phenacylpyridinium Cations

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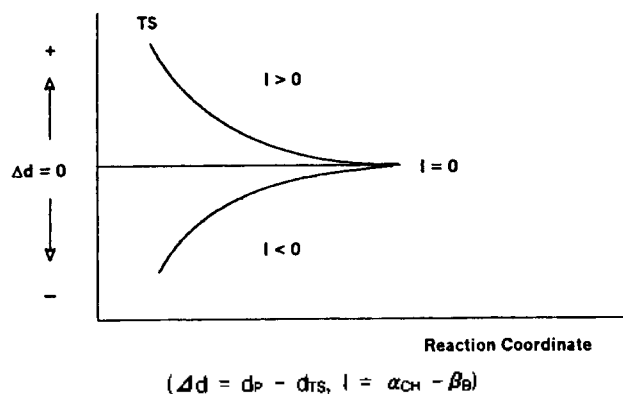*Received November 4, 1996*

Theoretical studies on the base-catalyzed deprotonation of 4-phenacylpyridimium cations, R^1-CO-CH$_2$-C$_5$H$_4$N-R^2, I (R^1=YC$_6$H$_4$- and R^2=CH$_3$), and II (R^1=C$_6$H$_5$ and R^2=CH$_2$C$_6$H$_4$Y) have been carried out with bases, NH$_3$ and XC$_6$H$_4$NH$_2$ using AM1 MO method. The Brønsted α values are 0.20 and 0.22 and the β_B values are 0.62 and 0.61, respectively for cations I and II. The negative I (=α-β_B) values obtained are in accord with the experimental results in aqueous solution, although the theoretical gas-phase α values for I are somewhat smaller than the experimental values in water due to neglect of solvation effect. It has been stressed that the Brønsted α is distorted not only by the lag in the resonance and solvation development in the carbanion, but also by the difference in the distance between the anionic center and substituents in the TS and in the product anion.
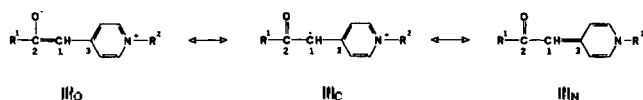
Introduction

In most chemical reactions, more than one process occurs concurrently: typically, bond formation or cleavage may be accompanied by solvation or desolvation, delocalization or localization of charge, hyperconjugative transfer of charge, etc. However, often these processes make unequal progress at the transiton state (TS) leading to an "imbalanced" TS.[1] In such situation, the progress of reaction at the TS depends on which process is adopted as the reaction coordinate.

Transition-state imbalances are a common phenomenon in many reactions including proton transfers involving most

$$(\Delta d = d_P - d_{TS}, \; I = \alpha_{CH} - \beta_B)$$

Scheme 1.

Scheme 2. (Numbering of carbon in shown).

Table 1. Proton affinities $(\Delta PA)^a$ of anilines and 4-phena-cylpyridinum cations calculated by the AM1 method

X (or Y)	Anilines	I	II
p-OCH₃	– 3.0	1.0	0.9
p-CH₃	– 2.0	0.7	0.7
H	0.0	0.0	0.0
p-CN	7.8	– 3.9	– 3.7
p-NO₂	15.3	– 7.2	– 6.6

^{a}HA$\rightleftharpoons$H$^+$+A$^-$, ΔPA=PA(X or Y) - PA(H): PA of X=H is 19.4 kcal mol^{-1} and of Y=H is 26.8 and 29.9 kcal mol^{-1} for (I) and (II), respectively (in this case, PA is calculated excepting the Gibbs energy of H$^+$).

types of C-H acids (a proton on C₁ in Scheme 2).[1c,2] According to the Principle of Nonperfect Synchronization (PNS) introduced by Bernasconi,[3] whenever resonance (and solvation) is involved as product (or reactant) stabilizing factor in a reaction, this factor will develop late (or be lost early) in the TS.

In the proton transfers the TS imbalance (I) is measured by I=α_{CH}-β_B, where α_{CH} is the Brønsted coefficient obtained by varying the pK_a of the carbon acid and β_B is obtained by varying the pK_a of the base (amine or oxyanion). The I value is in most cases positive, but in some cases the sign of I changes to negative.[2c,3] It is thought that in the imbalances with negative I, the site where the bulk of the negative charge ultimately resides (oxygen atoms of nitro, sulfonyl or carbonyl groups) is further away from the substituent in the TS than in the product anion, Δd ($=d_P$-d_{TS})<0, whereas it is closer in the TS than in the product anion (Δd> 0) for positive I.[2c] This can be readily visualized using a hypothetical adiabatic transition in which the TS is balanced with α_{CH}=β_B at all stages of reaction coordinate. If the substituent is closer to the anionic center in the TS than in the product α_{CH} will be greater leading to a positive I, whereas it is further away α_{CH} will be smaller than β_B and the I will be negative (Scheme 1). Thus the underlying cause for the imbalance is believed to be the same in all cases, and the change in the sign of I is due to a different location of the substituent relative to the anionic charge center within the molecule.

Recently, Bunting and Stefanidis[4] reported negative I (= α_{CH}-β_B) values for base-catalyzed deprotonations of 1-methyl-4-(Y-phenacyl)pyridinium, I (R^1=YC₆H₄- and R^2= CH₃ in Scheme 2), and 1-benzyl-4-(Y-phenacyl)pyridinium, II (R^1=C₆H₅ and R^2=CH₂C₆H₄Y in Scheme 2), cations in aqueous solution. Moreover, they found that the α_{CH} values obtained with the same amine base are different depending on whether the α_{CH} is determined by varying R^1 or by varying R^2, Scheme 2.

In order to gain information for the underlying causes of these TS Imbalance behaviors, we have carried out ex-

tensive MO theoretical studies using the AM1 method[5] on systems I and II with bases, [I (or II)+NH₃→I$^-$ (or II$^-$)+ NH₄$^+$]NH₃, and X-C₆H₄NH₂, [I (or II)+XC₆H₄NH₂→I$^-$ (or II$^-$)+XC₆H₄NH₃$^+$] by varying substituents X and Y (X=Y= p-OCH₃, p-CH₃, H, p-CN or p-NO₂).

Calculations

In this work, a semiempirical MO method, AM1,[5] was used in the calculations due to the complex reaction systems (16-31 heavy atoms are involved). All stationary point structures including TSs were fully optimized and were characterized by harmonic frequency calculations.[6] The Gibbs free energies of reaction, ΔG^o, and activation, $\Delta G^{\neq}$, were derived by adding $-T\Delta S^o$ and $-T\Delta S^{\neq}$ terms at 298 K to H^o and $\Delta H^{\neq}$ terms, respectively. All computations were performed using the MOPAC 6.0 program package.[7]

Results and Discussion

The relevant calculated values of energetics (kcal mol^{-1}) involved in the base-catalyzed deprotonation of cations I and II using NH₃ as a base are summarized in Table 1. Since negative charge develops in the TS, a stronger electron-withdrawing substituent (Y) accelerates the rates (or lowers $\Delta G^{\neq}$). The entropy effects vary very little and are approximately constant irrespective of the substituent Y.
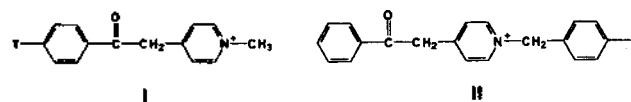

We have correlated the $\Delta G^{\neq}$ values in Table 1 with the proton affinities (PA) in Table 2 to determine the gas-phase α values, Eq. (4). The plots of $\Delta G^{\neq}$ vs PA (Figure 1), which are obviously equivalent to that of the Brønsted Eq. (1) as shown by Eqs. 2-3, yielded α_{CO}=0.20 (r=0.995) and α_{CN}=0.22 (r=0.992) for the cations I and II, respectively. The same values of α_{CO} (0.20) and α_{CN} (0.22) are obtained by the Leffler-Hammond plots,[8] Eq. (5), and also by the normalized ρ_n, α=ρ_n=ρ/ρ_{eq} values[9] where the ρ and ρ_{eq} values are obtained by Eqs. 6 and 7 using the normal σ constant, except for Y=p-NO₂ for which σ^-=1.24 was used. For cations I, ρ=0.82 (r=0.997) and ρ_{eq}=4.08 (r=0.999), while for cations II, ρ=0.82 (r=0.990) and ρ_{eq}=3.77 (r=0.999).

$$\delta \log k = -\alpha \cdot \delta(pKa) \tag{1}$$

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Table 2. Heats of formation (ΔH_f) of the stationary point species, activation parameters ($\Delta H^{\neq}$, $-T\Delta S^{\neq}$, $\Delta G^{\neq}$) and reaction energies (ΔH°, $-T\Delta S^{\circ}$, ΔG°) in kcal mol^{-1} for the cations I and II with NH_3 as a base

Cation	Y	ΔH_f					Acivation Parameters			Reaction Energies		
		R^a	RC^a	TS^a	PC^a	P^a	$\Delta H^{\neq}$	$-T\Delta S^{\neq b}$	$\Delta G^{\neq}$	ΔH°	$-T\Delta S^{\circ b}$	ΔG°
(I)	p-OCH$_3$	126.3	121.8	130.1	125.7	154.4	3.8	10.5	14.3	28.1	−0.3	27.8
	p-CH$_3$	157.4	152.9	161.1	156.7	185.0	3.7	10.5	14.2	27.6	−0.1	27.5
	H	165.8	161.2	169.4	165.0	192.7	3.6	10.5	14.1	26.9	−0.1	26.8
	p-CN	201.1	196.2	204.2	199.8	224.0	3.1	10.3	13.4	22.9	0.0	22.9
	p-NO$_2$	176.2	171.0	178.8	174.3	195.8	2.6	10.0	12.6	19.6	0.0	19.6
(II)	p-OCH$_3$	150.8	146.5	155.8	152.7	182.0	5.0	10.5	15.5	31.2	−0.4	30.8
	p-CH$_3$	181.4	177.1	186.3	183.1	212.3	4.9	10.6	15.5	30.9	−0.3	20.6
	H	189.9	185.5	194.6	191.2	220.0	4.7	10.6	15.3	30.1	−0.2	29.9
	p-CN	225.9	221.4	230.1	225.9	252.3	4.2	10.5	14.7	26.4	−0.2	26.2
	p-NO$_2$	201.6	197.0	205.1	200.2	224.9	3.5	10.3	13.8	23.3	0.0	23.3

^{a} R, RC, TS, PC and P denote reactant, reactant complex, transition state, product complex and product respectively. ^{b} At 298 K.
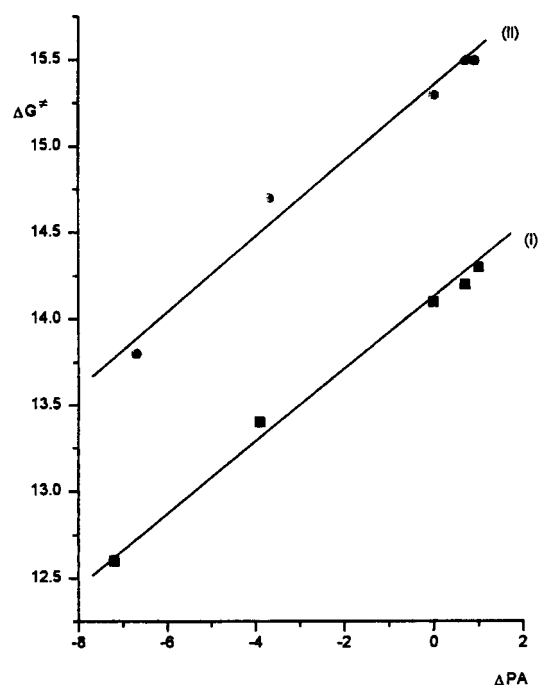
Figure 1. Plots of $\Delta G^{\neq}$ *vs* ΔPA for cations I and II with NH_3.

$$\delta \log k = -\delta \Delta G^{\neq} / 2.303RT \quad (2)$$

$$pK_a = -\log K_a = PA / 2.303RT \quad (3)$$

$$\delta \Delta G^{\neq} = \alpha \cdot \delta (PA) \quad (4)$$

$$\delta \Delta G^{\neq} = \alpha \cdot \delta \Delta G^{\circ} \quad (5)$$

$$-\delta \Delta G^{\neq} / 2.303RT = \rho \sigma \quad (6)$$

$$-\delta \Delta G^{\circ} / 2.303RT = \rho_{eq} \sigma \quad (7)$$

The Brønsted α values for the base-catalyzed deprotonation of cations I and II by the various amine catalyst in aqueous solution at 25 °C cluster in a range from α_{CO}=0.36 to 0.48 (average of 0.42) and α_{CN}=0.14-0.34 (average of 0.26), respectively.[4b] Thus our theoretical gas-phase α values, and especially the α_{CO} values are smaller than those for the experimental values in the aqueous solution. Al-
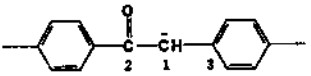
though the α_{CN} values vary 0.14-0.34 with the base used, the average value of 0.26 in aqueous solution[4b] is close to our theoretical gas-phase value of 0.22.

However, the average α_{CO} values (0.42) in aqueous solution is considerably larger than the gas-phase value of 0.20. Since the α value can be considered as a measure of the progress of reaction based on the negative charge development[3] in the TS along the reaction coordinate (the definition of Leffer-Hammond coefficient,[8] Eq. 5, and $\rho_n = \rho/\rho_{eq}$[9]), this means that the TS is reached much earlier in the gas phase than in aqueous solution. This is reasonable because the hydrated carbonyl oxygen anion (III_o) will be much more stable in water. Even though the PNS requires that the solvation of the anionic product lags behind the proton transfer,[3] the partial solvation will help stabilize the TS leading to a somewhat later TS than the TS in the gas-phase where there is no product stabilizing effect is available. In contrast to an anionic product in III_O, there is no localized charge in III_N so that no such solvation effect is available. In fact, the positive charge on the reactant pyridine nitrogen becomes neutralized in the product, III_N, and according to the PNS desolvation of the reactant with take place earlier in the TS[3] so that solvation effect is practically absent for the experimental α_{CN} values; this may be the reason why the two α_{CN} values obtained in aqueous solution and in the gas phase are similar in contrast to the considerably different α_{CO} values in the two different phases due to solvation effect. The efficiency of transmission of (Y) substituent effects in the TS for the two cations, I and II, seem to be similar (for both cases, ρ=0.82), so that the difference in α ($\Delta \alpha = \alpha_{CO} - \alpha_{CN} > 0$) is not originated from the different degree of transmission efficiency of substituent effects; one would expect a lower efficiency in cation II than I, since the developing anionic center in the TS is further away from the substituent in cation II. The resonance delocalization and positive charge neutralization effect of the pyridine ring seem to be enough for overcoming the long-distance handicap.

Structurally, however, the progress of double bond formation in the TS, as defined by $\% \Delta l^{\neq} = (l_{TS} - l_R)/(l_P - l_R) \times 100$, where l_{TS}, l_R and l_P are the bond length in the TS, reactant and product, respectively,[10] is 40-42% and 45-46% for $C_1 = C_2$ and $C_1 = C_3$ in cation I and 43-46% and 46-49% for $C_1 =$

C_2 and $C_1=C_3$ in cation II (Table 3). The structural reorganization is overall *ca.* twice of the α values ($\alpha_{CO} \cong \alpha_{CN} \cong 0.20$) which were derived based on energetics. Annihilation of positive charge on the N atom of pyridine ring always leads to somewhat more advanced change in $C_1=C_3$ than in $C_1=C_2$. What is surprising is that the structural changes (the negative charge increase on the N atom has also approximately 40% progressed in the TS) is much more (*ca.* twice) advanced in the TS than the energetic changes judg-

ed by the α values. The lower degree of reaction progress based on the α values than the progress of structural changes in the TS is clearly due to the longer distance between the anionic charge center and substituents in the TS (d_{TS}) than in the product anion (d_P), Δd ($=d_P-d_{TS}$)<0. The anionic charge center moves to $C_2=O$ (III_O) and N on pyridine (III_N) from C_1 (III_C) in I and II, respectively, on going from the TS to the product anion. As noted above, the susceptibility of the anionic charge to substituent changes will be smaller in the TS (ρ_{kin}) than in the product (ρ_{eq}) leading to lower values of $\Delta\alpha<0$ than would be expected for the ideal case at the same distance, $\Delta d=0$ ($\alpha=\rho_n=\rho_{kin}/\rho_{eq}$, where $\rho_{kin}<\rho_{true}$ and ρ_{true} is the value that would have been observed). Conversely if the distance is shorter in the TS than in the product, $\Delta d>0$, an exalted α value will be observed $\Delta\alpha>0$.[2c] This analysis shows that the exalted α values observed in deprotonation of many nitroalkanes are partly due to the shorter distance between developing anionic center and the substituents in the TS than in the product anion, $\Delta d>0$, in addition to the imbalanced TS induced by delayed development of resonance and solvation.

Since progress of structural reorganization is approximately 40% along the reaction coordinate, *i.e.*, $\alpha_{str} \cong 0.4$, which is reduced to *ca.* 20% ($\alpha \cong 0.2$) upon inclusion of $\Delta\alpha<0$ due to $\Delta d<0$, the $\Delta\alpha$ is *ca.* -0.2 since, $\Delta\alpha=\alpha_{total}-\alpha_{str} \cong 0.2-0.4= -0.2$; the α value due to the simple distance change is therefore *ca.* 0.2.

We have used deprotonation of the same two series of cations, I and II, in the dedermination of the β_B values using substituted anilines as bases in Eq. (8), where PA is the PA of substituted anlines. The energetics are summarized in Table 4. The slope, β_B, of the plot of $\Delta G^{\ne}$ against PA gave 0.62 and 0.61, respectively, for cation systems I and II. The experimental β_B values have been reported to range from $\beta_B=0.53$ to 0.55.[4b] The slightly greater theoretical value of β_B (by *ca.* 0.06-0.09) than the experimental value in aqeous solution is quite reasonable, since desolvation required in water during or prior to protonation of the base is known to reduce the β_B values in aqueous solution.[11] The theoretical TS imbalance, $I=\alpha-\beta_B \cong 0.20-0.60=-0.40$, is thus negative and the magnitude (I=-0.4) seems to be well within the range of I expected.[3,4b]

$$\delta\Delta G^{\ne} = -\beta_B\,\delta(PA) \tag{8}$$

Table 3. Some AM1 bond lengths (Å)

Y		Cation I		Cation II	
		$l(C_1-C_2)$	$l(C_1-C_3)$	$l(C_1-C_2)$	$l(C_1-C_3)$
p-OCH₃	R	1.517	1.483	1.516	1.483
	TS	1.492	1.427	1.487	1.424
	P	1.454	1.361	1.453	1.362
	$\%\Delta l^{\ne a}$	39.7%	45.9%	46.0%	48.8%
p-CH₃	R	1.517	1.483	1.516	1.483
	TS	1.491	1.426	1.487	1.425
	P	1.453	1.361	1.453	1.362
	$\%\Delta l^{\ne a}$	40.0%	46.7%	46.0%	47.9%
H	R	1.517	1.483	1.516	1.483
	TS	1.490	1.427	1.488	1.425
	P	1.453	1.362	1.453	1.361
	$\%\Delta l^{\ne a}$	42.2%	46.3%	44.4%	47.5%
p-CN	R	1.515	1.484	1.516	1.483
	TS	1.488	1.429	1.490	1.426
	P	1.450	1.363	1.455	1.360
	$\%\Delta l^{\ne a}$	41.5%	45.5%	42.6%	46.3%
p-NO₂	R	1.514	1.484	1.517	1.483
	TS	1.486	1.431	1.491	1.427
	P	1.447	1.365	1.456	1.360
	$\%\Delta l^{\ne a}$	41.8%	44.5%	42.6%	45.5%

a $\%\Delta l^{\ne}=100 \cdot (l_{TS}-l_R)/(l_P-l_R)$. Approximately the same values are obtained when the progress of reaction is defined alternatively using bond order (n) changes: $\%\Delta n^{\ne}=100[\exp(-l_{TS}/0.6)-\exp(l_R/0.6)]/[\exp(-l_P/0.6)-\exp(-l_R/0.6)]$: (a) G. P. Ford and C. T. Smith, *J. Am. Chem. Soc.* 1987, *109*, 1325. (b) S. S. Glad and F. Jensen, *J. Chem. Soc., Perkin Trans. 2* 1994, 871.

Table 4. Heats of formation (ΔH_f) of the stationary point species, activation parameters ($\Delta H^{\ne}$, $-T\Delta S^{\ne}$, $\Delta G^{\ne}$) and reaction energies (ΔH°, $-T\Delta S^{\circ}$, ΔG°) for cation I and II with XC₆H₄NH₂ (kcal mol⁻¹) as bases

Cation	X	ΔH_f					Activation Parameters			Reaction Energies		
		R	RC	TS	PC	P	$\Delta H^{\ne}$	$-T\Delta S^{\ne a}$	$\Delta G^{\ne}$	ΔH°	$-T\Delta S^{\circ a}$	ΔG°
(Ia)	p-OCH₃	156.5	149.3	163.2	155.6	178.6	6.7	11.6	18.3	22.1	-0.8	21.3
	p-CH₃	186.0	181.6	193.6	186.2	209.5	7.6	11.2	18.8	23.5	-1.2	22.3
	H	193.5	189.6	201.7	194.8	218.6	8.2	11.2	19.4	25.1	-0.8	24.3
	p-CN	223.8	221.2	237.1	232.1	257.1	13.3	11.6	24.9	33.3	-1.2	32.1
	p-NO₂	194.6	179.8	212.2	208.8	235.2	17.6	11.8	29.4	40.6	-1.0	39.6
(IIa)	p-OCH₃	180.6	173.9	188.5	181.9	205.9	7.9	11.6	19.5	25.3	-0.9	24.4
	p-CH₃	210.1	205.2	218.6	212.6	236.8	8.5	11.5	20.0	26.7	-1.2	25.5
	H	217.6	214.0	226.8	221.3	246.0	9.2	11.3	20.5	28.4	-0.9	27.5
	p-CN	247.9	244.9	262.4	258.4	284.5	14.5	11.4	25.9	36.6	-1.2	35.4
	p-NO₂	218.7	204.7	237.7	235.2	262.6	19.0	11.4	30.4	43.9	-1.1	42.8

a At 298 K.

One may wonder what will be the true I value if we remove the part due to the distance factor. The I value becomes smaller but still is negative, $I \cong 0.4\text{-}0.6) = -0.2$, based on the progress of reaction judged by the structural reorganization of *ca.* 40%. We note that the structural reorganization, mainly consisting of resonance structure development, is delayed by *ca.* 20% compared to the proton transfer to the base.[3]

The current work demonstrates that the Brønsted type coefficient α obtained by varying the pK_a of the carbon acid is distorted not only by the lag in the resonance and solvation development in the carbanion, but also by the difference in the distance between the anionic center and substituents (d) in the TS (d_{TS}) and in the anionic product (d_P), $\Delta d = d_P\text{-}d_{TS}$; Thus for $\Delta d < 0$ α is depressed, $\Delta\alpha < 0$, and for $\Delta d > 0$ α is exalted $\Delta\alpha > 0$. Although the TS imbalance found in this work has negative sign, $I = \alpha - \beta < 0$, the structural reorganization nevertheless lags behind the proton transfer. Although such distance effect on the negative I has been proposed, no concrete evidence has ever been presented. For the first time, this work does provide such theoretical evidence. In future discussion of the TS imbalance, I, the exhalted ($\Delta\alpha > 0$) or depressed ($\Delta\alpha < 0$) α values originating from the simple distance difference should be carefully accounted for in assessing the true TS imbalance originating the delayed or early structural and solvation reorganization.

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