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Rate Constants for Hydrogen Atom Transfer Reactions from Bis(cyclopentadienyl)titanium(III) Chloride-Complexed Water and Methanol to an Alkyl Radical

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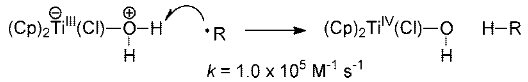

Rate constants for hydrogen atom transfer reactions of the water, deuterium oxide, and methanol complexes of bis(cyclopentadienyl)titanium(III) chloride with the secondary alkyl radical 1-cyclobutyldodecyl (**2**) were determined using indirect kinetic methods. The rate constant for reaction of $Cp_2Ti^{III}Cl-H_2O$ in THF at ambient temperature was $1.0 \times 10^5\ M^{-1}\ s^{-1}$, and the kinetic isotope effect was $k_H/k_D = 4.4$. In benzene containing 0.95 M methanol, the rate constant for reaction of the $Cp_2Ti^{III}Cl-MeOH$ at ambient temperature was $7.5 \times 10^4\ M^{-1}\ s^{-1}$. An Arrhenius function for reaction of the $Cp_2Ti^{III}Cl-H_2O$ complex in THF was $\log k = 9.1 - 5.5/2.3RT$ (kcal/mol). The entropic term for reaction of $Cp_2Ti^{III}Cl-H_2O$ was normal, whereas the entropic term previously found for reaction of the Et_3B-H_2O complex with radical **2** was unusually small (Jin, J.; Newcomb, M. *J. Org. Chem.* **2007**, *72*, 5098).

Introduction

Radical chain reactions have become commonplace in organic synthetic applications in recent years. Often, the final step in a productive radical chain sequence is hydrogen atom transfer to give a reduced product, and the most commonly used hydrogen atom transfer agents have been trialkyltin hydrides. Tin hydrides react with radicals with rate constants that are well suited for radical chain reactions,[1] but there has been an increasing emphasis on the development of alternative hydrogen transfer agents due in large part to concerns about the toxicity of tin-containing compounds. Some of the more exciting advances in this direction involve the use of water and alcohols as safe "green" hydrogen atom transfer agents.[2−4] The high O−H bond dissociation energies[5] (BDEs) of alcohols (ca. 105 kcal/mol) and water (118 kcal/mol) suggest that hydrogen atom transfers from these sources to carbon-centered radicals will be too slow to be useful, but Lewis acid complexed alcohols and water have much reduced O−H BDEs[6] and can react with alkyl radicals rapidly.

In studies of radical chemistry triggered by bis(cyclopentadienyl)titanium(III) chloride reductions of epoxides or α,*β*-unsaturated ketones, Barrero et al. demonstrated that water complexed with $Cp_2Ti^{III}Cl$ was a radical reducing agent,[7] and Moisan et al. found that methanol complexed with $Cp_2Ti^{III}Cl$ similarly reacted in radical reductions.[8] More recently, Cuerva et al. reported more examples of $Cp_2Ti^{III}Cl$−water reductions of radicals as well as computational results that indicated that the O−H BDE in the complex was only 49 kcal/mol.[9] In recent works, we reported rate constants for hydrogen atom transfer reactions of water and methanol complexed with triethylborane[10,11] using radical clock kinetic methods.[12,13] In the present work, we report similar kinetic studies of reactions of a secondary alkyl radical with the water and methanol complexes of $Cp_2Ti^{III}Cl$.

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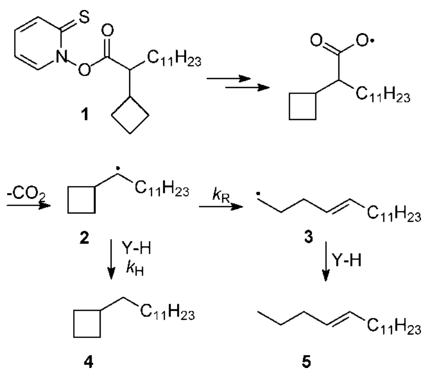
SCHEME 1



Results and Discussion

In radical reactions initiated with Cp_2TiCl, the radicals typically are derived by reductions of epoxides or enones, and the overall reactions can be in nonchain processes. In order to employ indirect kinetic methods,[14] we used a PTOC ester[15,16] as a radical precursor for chain reactions. The reaction sequence shown in Scheme 1 is well studied.[11] PTOC ester **1** reacted in initiation reactions or in chain reactions to form initially an acyloxyl radical that rapidly decarboxylated to give the 1-cyclobutyldodecyl radical clock (**2**). Radical **2** reacted with the hydrogen atom donor to give cyclobutane **4** in competition with ring opening to give radical **3**. Radical **3** also reacted with the hydrogen atom donor to give ring-opened product **5**. Rate constants for ring opening of radical **2** are available,[11] and the ratio of products **4** to **5** obtained at the end of the reaction can be used with the rate constant for rearrangement (k_R) to give the unknown rate constant for hydrogen atom transfer (k_H).[13] In principle, the study might be complicated due to complexation of the PTOC ester with the Lewis acid Cp_2TiCl, but that was not a problem in practice. The PTOC ester reactions were initiated with visible light irradiation, and reactions were analyzed for completion by TLC.

PTOC esters are valuable radical precursors in part because they react readily in chain propagation reactions with a wide range of radicals.[15] This reactivity establishes a competition reaction for the alkyl radicals that react with the PTOC ester to give alkyl pyridyl sulfides in addition to alkanes from H-atom trapping. The rate constant for reaction of a primary alkyl radical with a PTOC ester at ambient temperature is 1.3×10^6 M^{-1} s^{-1}.[17] We used initial concentrations of PTOC ester **1** that were ca. 10−20 mM, and assuming that radicals **2** and **3** react with precursor **1** with a rate constant somewhat greater than 1×10^6 M^{-1} s^{-1}, the "self-trapping" reactions will have pseudo-first-order rate constants on the order of 1×10^4 s^{-1}. Reduced yields of alkane products found in some of our kinetic studies undoubtedly reflect competition of the self-trapping reaction that diverted a portion of the radicals.

A series of reactions was conducted with PTOC ester **1** in benzene solvent with freshly prepared[18] $Cp_2Ti^{III}Cl$ and D_2O. In these reactions, the concentration of $Cp_2Ti^{III}Cl$ was varied by a factor of 7, and the ratio of the formal concentration of titanium reagent to D_2O was maintained at 1:1. For all reactions, the sum of the yields of hydrocarbons **4** and **5** was somewhat less than 30%, the ratio of [**4**]/[**5**] was consistently 1.6, and ca. 50% deuterium incorporation was found in the hydrocarbon products. These results indicate that only a low concentration of trapping agent was present in the reactions, allowing significant trapping of alkyl radicals by the PTOC ester radical precursor as well as a significant amount of radical−radical reactions. These results are not consistent with the observations of efficient radical trapping by water and methanol complexes of the titanium reagent.[7−9] We conclude that only low concentrations of the desired titanium(III) reagent were obtained in the noncoordinating solvent benzene, where it is known that the reagent exists (possibly largely) as the chloride-bridged dimer[18] (Scheme 2).

SCHEME 2

TABLE 1. Products Ratios and Yields from Reactions of Radical 2 with $Cp_2Ti^{III}Cl-H_2O$ in THF[a]

$[Cp_2Ti^{III}Cl]$ (M)	$[H_2O]$ (M)	% yield[b]	[**4**]/[**5**]
0.06	0.41	63	4.64
0.06	0.41	64	4.59
0.12	0.47	70	7.07
0.12	0.47	70	6.92
0.18	0.53	65	11.10
0.18	0.53	65	11.06
0.24	0.59	94	13.52
0.24	0.59	94	13.70

[a] Reactions of PTOC ester **1** in THF at 23 °C. [b] Yield of products **4** plus **5**.

In the coordinating solvent THF, the titanium complex behavior was consistent with reasonably efficient radical trapping by the $Cp_2Ti^{III}Cl-$water complex as previously reported.[9] A series of reactions of PTOC ester **1** conducted in THF solvent with varying concentrations of the titanium reagent and water gave the results that are listed in Table 1. At low concentrations of the titanium reagent, considerable amounts of radical−radical reactions and reactions of radicals with precursor **1** are indicated by the limited total yield of products **4** and **5**. At higher concentrations of titanium reagent, the high yields of hydrocarbon products and the large amount of trapped cyclic product **4** relative to rearranged product **5** indicate that the trapping reactions were relatively efficient. Figure 1 shows the ratio of product **4** to product **5** as a function of the concentration of titanium reagent in the THF studies.

The reaction of radical **3** with the $Cp_2Ti^{III}Cl-D_2O$ complex in THF solvent was evaluated in a similar manner, and the results are collected in Table 2 and are shown in Figure 1. In these reactions, the combined yields of products **4** and **5** were not as great as those found in reactions with the water complex, most likely because the trapping reaction with D_2O was less competitive with the PTOC ester self-trapping reaction.[17]

In our studies, an excess of titanium reagent was employed, and a greater excess of water was present. The results of Cuerva et al.[9] demonstrate that water binds efficiently with the titanium reagent in THF solvent, and it is reasonable to assume that the

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(15) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.

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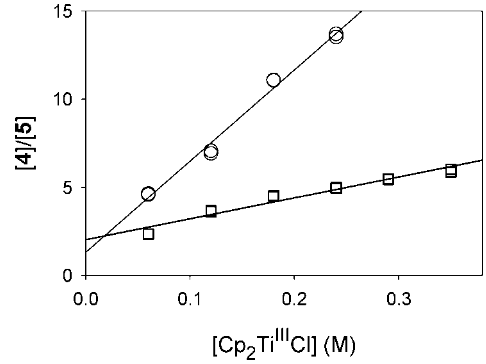

FIGURE 1. Product ratios from reaction of radical **2** in THF at 23 °C with the $Cp_2Ti^{III}Cl-H_2O$ complex (circles) and with the $Cp_2Ti^{III}Cl-D_2O$ complex (squares).

TABLE 2. Product Ratios and Yields from Reactions of Radical 2 with $Cp_2Ti^{III}Cl-D_2O$ THF[a]

[$Cp_2Ti^{III}Cl$] (M)	[D_2O] (M)	% yield[b]	% D[c]	[**4**]/[**5**]
0.06	0.41	52	70	2.35
0.06	0.41	56	70	2.35
0.12	0.47	62	72	3.67
0.12	0.47	67	72	3.63
0.18	0.53	47	72	4.52
0.18	0.53	49	72	4.48
0.24	0.59	58	72	4.98
0.24	0.59	59	72	4.94
0.29	0.65	58	72	5.48
0.29	0.65	59	72	5.45
0.35	0.71	59	71	5.87
0.35	0.71	59	72	6.02

[a] Reactions of PTOC ester **1** in THF at 23 °C. [b] Yield of products **4** plus **5**. [c] Percentage of deuterium incorporation in products **4** and **5**.

titanium reagent was essentially fully complexed by water in our studies. Therefore, the results in Figure 1 are described by eq 1, where k_T is the second-order rate constant for trapping radical **2**, k_R is the rate constant for rearrangement of radical **2**, [Ti] is the concentration of titanium reagent, and C is the intercept of the plot on the Y axis. The slope of the plot for the $Cp_2Ti^{III}Cl-H_2O$ complex in Figure 1 is $(k_T/k_R) = 52 \pm 5$ M^{-1} (error at 2σ). Using a rate constant for rearrangement of radical **2** at 23 °C of $k_R = 1.9 \times 10^3$ s^{-1},[11] we calculate a second-order rate constant for reaction of $Cp_2Ti^{III}Cl-H_2O$ of $k_T = (1.0 \pm 0.1) \times 10^5$ M^{-1} s^{-1} at 23 °C. For the $Cp_2Ti^{III}Cl-D_2O$ complex, the slope is $(k_T/k_R) = 11.9 \pm 1.6$ M^{-1} (error at 2σ), and the rate constant for reaction of the complex with alkyl radical **2** is $k_T = (2.3 \pm 0.3) \times 10^4$ M^{-1} s^{-1} at 23 °C. The H/D kinetic isotope effect is $k_H/k_D = 4.4 \pm 0.7$. This value for the KIE assumes that the reactions of titanium−water complexes are the only reactions changing rates with concentration, which might not be completely correct, but the value is reasonable and reinforces the conclusion that the titanium−water complex indeed is a hydrogen atom donor for the radical.

$$[\mathbf{4}]/[\mathbf{5}] = C + (k_T/k_R)[\mathrm{Ti}] \qquad (1)$$

The intercepts of the plots in Figure 1 are $C = 1.3 \pm 0.7$ for the water complex and $C = 2.0 \pm 0.4$ for the D_2O complex (errors at 2σ). If the ring opening reaction of radical **2** was reversible, then these values would reflect in part the rate constants for the cyclization of **3** and the trapping rate constants for the hydrogen atom donors.[13] The ring opening of radical **2** is known to be essentially irreversible,[11] however, and the intercepts are ascribed entirely to reaction of radical **2** with THF solvent. From the values of C and the rate constant for ring opening of radical **2**, one calculates that the THF trapping reaction of radical **2** has pseudo-first-order rate constants in the range of $(2-4) \times 10^3$ s^{-1} at 23 °C. Previously, pseudo-first-order rate constants for reactions of alkyl radicals in THF at 50 °C were found to be in the range of $(2-6) \times 10^3$ s^{-1},[17,19] in good agreement with the values found here.

TABLE 3. Product Ratios and Yields from Reactions of Radical 2 with $Cp_2Ti^{III}Cl-MeOH$ in Benzene[a]

[$Cp_2Ti^{III}Cl$] (M)	% yield[b]	[**4**]/[**5**]
0.015	53	0.77
0.015	55	0.77
0.029	46	1.44
0.029	46	1.44
0.059	50	3.13
0.059	47	3.10
0.088	56	4.19
0.088	56	4.20
0.118	59	5.24
0.118	59	5.36

[a] Reactions of 12−15 mM PTOC ester **1** in benzene containing 0.95 M methanol at 22 °C. [b] Yield of products **4** plus **5**.

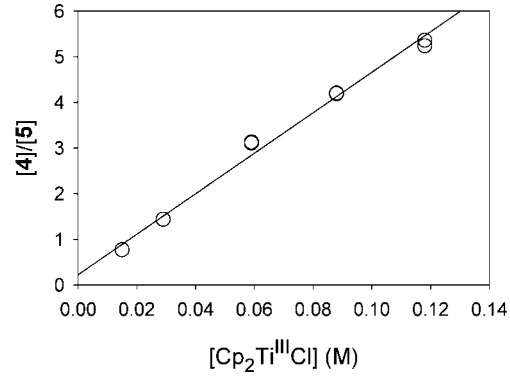

FIGURE 2. Product ratios from reaction of radical **2** in benzene containing 0.95 M methanol at 22 °C with the $Cp_2Ti^{III}Cl-MeOH$ complex.

We concluded above that reaction of the titanium(III)−water complex as a hydrogen atom donor was not well behaved in benzene solvent because the titanium species was likely sequestered in part as an unreactive chloride-bridged dimer.[18] If that conclusion is correct, then it should be possible to dissociate the dimeric titanium species in benzene with an adequate amount of a donor cosolvent. Indeed, we were able to accomplish this by adding methanol to benzene solutions of the titanium species. A series of reactions was conducted with PTOC ester **1** reacting in the presence of varying amounts of $Cp_2Ti^{III}Cl$ in benzene containing ca. 1 M methanol. The results are collected in Table 3, and the product ratios as a function of the concentration of the titanium reagent are shown graphically in Figure 2. From the slope of the plot in Figure 2, $(k_T/k_R) = 44 \pm 3$ M^{-1} (error at 2σ), and the rate constant for reaction of the $Cp_2Ti^{III}Cl-MeOH$ complex with alkyl radical **2** is $k_T = (7.5 \pm 1.0) \times 10^4$ M^{-1} s^{-1}. The intercept in Figure 2 is within experimental error of zero (0.2 ± 0.2) as expected for reaction in a solvent that is a poor hydrogen atom donor. The similarity of the kinetic values for the water and methanol complexes of the titanium(III) reagent further reinforces the mechanistic conclusion that the hydrogen donors are complexes of the titanium reagent with hydroxylic species.

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SCHEME 3

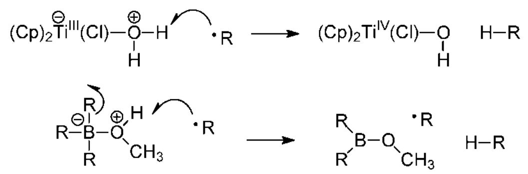

TABLE 4. **Product Ratios and Yields from Reactions of Radical 2 with $Cp_2Ti^{III}Cl-H_2O$ in THF**[a]

temp (°C)	$[Cp_2Ti^{III}Cl]$ (M)	% yield[b]	[**4**]/[**5**]
0.6	0.118	91	23.6
	0.118	94	22.8
	0.118	96	23.0
23.3	0.118	70	7.07
	0.118	70	6.92
	0.176	65	11.1
	0.176	65	11.1
	0.235	94	13.5
	0.235	94	13.7
36.0	0.118	79	4.24
	0.118	79	4.24
50.1	0.118	82	2.42
	0.118	82	2.42

[a] Reactions of PTOC ester **1** in THF containing 0.73 M H_2O. [b] Yield of products **4** plus **5**.

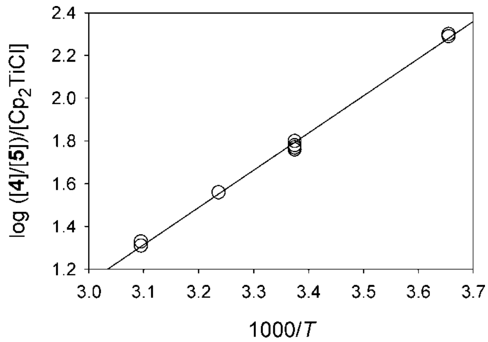

FIGURE 3. Relative Arrhenius function for reactions of alkyl radical **2** with $Cp_2Ti^{III}Cl-H_2O$ complex.

In studies of reactions of the Et_3B complexes of water and methanol as hydrogen atom donors, we found unusual behavior in that the entropic demand of the H-atom transfer from the $Et_3B-MeOH$ complex was very low,[10] and it was of interest to determine the activation parameters for reaction of the $Cp_2Ti^{III}Cl-H_2O$ complex with radical **2** for comparison. A series of reactions of PTOC ester **1** in THF was conducted over the temperature range of 0.6 to 50 °C, and the results are collected in Table 4 and shown graphically in Figure 3. Note that in Figure 3 we have plotted log([**4**]/[**5**]) divided by the concentration of the titanium reagent as a function of $1/T$. In this type of analysis, the concentration of the titanium reagent is factored out, and Figure 3 shows a relative Arrhenius function for trapping and ring opening of radical **2**. That is, the derived parameters are differences in log A and the activation energies, and the results are given in eq 2. Combination of these results with the previously reported[11] Arrhenius function for ring opening of radical **2** (eq 3) gives the Arrhenius function for trapping radical **2** by the $Cp_2Ti^{III}Cl-H_2O$ complex that is shown in eq 4. In eqs 2−4, activation energies are in kcal/mol and errors are 1σ. Equation 4 gives a rate constant for reaction of the $Cp_2Ti^{III}Cl-H_2O$ at 23 °C of $k_T = 1.1 \times 10^5\ s^{-1}$, in excellent agreement with the value of $1.0 \times 10^5\ s^{-1}$ found from the data in Table 1.

$$\log(k_T/k_R) = (-4.1 \pm 0.1) - (-8.0 \pm 0.1)/2.3RT \quad (2)$$

$$\log k_R = (13.2 \pm 0.4) - (13.5 \pm 0.6)/2.3RT \quad (3)$$

$$\log k_T = (9.1 \pm 0.4) - (5.5 \pm 0.6)/2.3RT \quad (4)$$

The activation parameters, and specifically the entropic term (log A = 9.1), for the hydrogen atom transfer reaction of the $Cp_2Ti^{III}Cl-H_2O$ complex are quite “normal” for a second-order hydrogen atom transfer reaction[1,13] and, indeed, for most second-order reactions. It is noteworthy that the entropic term for hydrogen atom transfer from the $Et_3B-MeOH$ complex to radical **2** was unusual with log A = 7.2, indicating a loosely organized transition state for the H-atom transfer reaction. These values suggest much different reaction pathways for the Lewis acid complexed hydroxylic species (Scheme 3). In the normal reaction of the $Cp_2TiCl-H_2O$ complex, the reactant is oxidized in an essentially stoichiometric reaction that results in a radical chain termination process. For the trialkylborane−water complex, the small entropic penalty in the transition state suggests that a fragmentation reaction coincides with the H-atom transfer reaction, presumably homolytic fragmentation of an alkyl group from the borane in a radical chain propagation reaction.

In conclusion, the rate constants for reactions of $Cp_2Ti^{III}Cl$-complexed water and methanol with a secondary alkyl radical have been determined. At ambient temperature in THF, the titanium(III) reagent complexed with water and deuterium oxide reacts with the secondary alkyl radical **2** with rate constants of 1.0 × 10 and $2.3 \times 10^4\ M^{-1}\ s^{-1}$, respectively. In benzene containing 0.95 M methanol, the $Cp_2Ti^{III}Cl-MeOH$ complex reacts with a rate constant of $7.5 \times 10^4\ M^{-1}\ s^{-1}$. The titanium(III) reagent apparently activates water and methanol more strongly than Et_3B with the result that the H-atom transfer reaction of the $Cp_2Ti^{III}Cl-H_2O$ complex is 5 times as fast as the H-atom transfer reaction of Et_3B-H_2O at room temperature. The Arrhenius function for reaction of $Cp_2Ti^{III}Cl-H_2O$ had a normal entropic term; however, the unusually low entropic term for the borane−water complex[10] leads to more efficient hydrogen atom transfer trapping by this species at low temperatures.

Radical reductions by H-atom transfer from water or alcohol complexes of $Cp_2Ti^{III}Cl$ will be useful when radicals are generated by reduction of epoxides or α,β-unsaturated ketones. In a general sense, it is noteworthy that the rate constants found in this work are about 1 order of magnitude smaller than those for radical reduction reactions of tin hydrides and similar to those for reactions of $((CH_3)_3Si)_3SiH$.[1] The reactions are fast enough to be used in many radical chain reaction sequences, and the kinetics illustrate a large degree of O−H bond activation possible by complexation of simple hydroxylic compounds with a strong Lewis acid.

Experimental Section

The syntheses of PTOC ester **1** were reported previously.[11] The products from H-atom trapping of radicals **2** and **3**, dodecylcyclobutane (**4**), and *trans*-4-hexadecane (**5**) were identified by GC and GC−mass spectrometry as previously reported.[10]

Kinetic Studies. Solutions of $Cp_2Ti^{III}Cl$ in anhydrous THF were prepared from $Cp_2Ti^{IV}Cl_2$ by the method of Rajanbabu and Nugent.[18] These solutions were transferred by syringe to degassed THF solutions containing PTOC ester **1** (0.05 mmol) and water or deuterium oxide (2 mmol) in 1.75 mL of THF. The resulting mixture was shielded from light, degassed by He sparging for 30 min, and thermally equilibrated in a temperature-controlled bath for variable temperature studies. The shield was removed, and the mixture was irradiated with visible light for ca. 6 h. An internal standard of dodecane was added, and the mixture filtered through a short pad of silica gel with hexane elution. The product mixture was analyzed by GC on a low polarity column (DB-5 bonded phase, 15 m × 0.53 mm). Products **4** and **5** were identified by GC retention times and mass spectral fragmentation patterns in comparison to those of authentic samples.

For reactions conducted in benzene−methanol, the $Cp_2Ti^{III}Cl$ was prepared in benzene by the above procedure and added to benzene solutions containing PTOC ester **1** (0.05 mmol) and methanol (4 mmol) to give solutions of total volumes of 4.2 mL that were then treated as above.

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Supporting Information Available: NMR spectra of PTOC ester **1** and hydrocarbons **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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