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Demethylation reactions of phosphate esters catalysed by complexes of polyether ligands with metal iodides

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Metal ion catalysis has been observed in demethylation reactions of methyl di(*para*-substituted phenyl)phosphate esters **1**–**4** promoted by complexes of polyether ligands **5**–**7** with alkali metal iodides MI (M = Li, Na, K) in low polarity media (chlorobenzene, 1,2-dichlorobenzene). The catalytic effect is found to depend on both the metal ion charge density and the ligand topology. Rate constants increase, in the order $K^+ < Na^+ < Li^+$, with the complexes of crown ether **5** and PEG **6**, whereas they are much lower and independent of the cation with the cryptates of **7**. Reaction rates are favored by electron-withdrawing substituents, with Hammett ρ-values that increase with decreasing Lewis acid character of the cation ($Li^+ < Na^+ < K^+$) or when the charge of the latter is shielded by a good complexing agent like cryptand **7**. Kinetic data are explained on the basis of a concerted "push–pull" mechanism.

Introduction

Macrocyclic and open chain polyethers (crown ethers, cryptands, polyethylene glycols) are synthetic ligands of particular interest owing to their unique ability to solubilize metal salts in organic media, even of low polarity, by formation of stable and highly structured inclusion complexes.[1,2] In these complexes the anion is remarkably activated due to the limited interaction with both the bulky complexed cation and the reaction medium. The anionic reactivity is mainly determined by the ability of the ligand to bind effectively the cation, and hence to activate the ion-paired anion, increasing in the order: polyethylene glycol < crown ether ≪ cryptand.[1,2]

The topology of the ligand also plays a fundamental role in reactions where metal ions are involved in the activation process ("electrophilic catalysis"). In this case the cation complexation by the host ligand is expected to cause rate decrease through inhibition of cation participation.[1b,3] In early studies we revealed cation assistance in nucleophilic substitution reactions of alkylsulfonates catalysed by complexes of metal iodides with polyether ligands in chlorobenzene.[4] Our results showed that catalysis is inhibited by good complexing agents such as cryptands whereas it is favored by less efficient ligands (crown ethers or polyethylene glycols).[4]

Recently, we reported on metal ion effects in demethylation reactions of phosphinic esters promoted by complexes of macrocyclic and open chain polyethers with alkali and alkaline-earth metal salts in low polarity media.[5] Demethylation reactions are of particular interest since the final removal of the protecting group (usually a methyl group) from the phosphate function of the substrate often represents the final step of the synthesis of oligonucleotides with the phosphotriester method.[6–8] Phosphate esters are known to be an integral part of a number of biologically active molecules ranging from DNA and ATP to pesticides up to nerve agents.[6–9] As a consequence, the reactions that involve phosphate esters play leading roles in the chemical processes of life.[6–9]

In this paper we present a kinetic study of the effect of the cation in demethylation reactions of methyl di(*para*-substituted phenyl)phosphates **1**–**4** promoted by complexes of polyether ligands PHDB18-crown-6 **5**, PEG400Me$_2$ **6** and cryptand [2.2.2,C$_{10}$] **7** with alkali metal and ammonium iodides MI (M = Li, Na, K, NH$_4$) in low polarity solvents (chlorobenzene, 1,2-dichlorobenzene). In order to obtain a comparison with the corresponding uncatalysed reactions we also performed kinetic experiments with the lipophilic quaternary onium salt Hexyl$_4$N$^+$I$^-$.

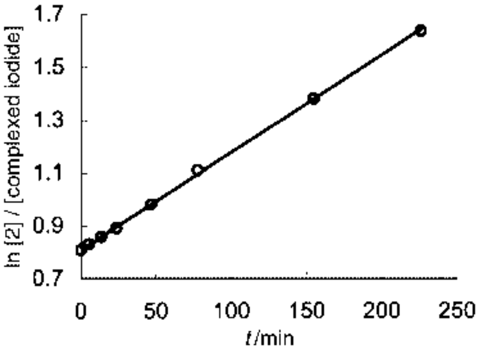

Fig. 1 Second-order plot for the reaction of (4-CH$_3$C$_6$H$_4$O)$_2$P(O)-OCH$_3$ **2** (1.08×10^{-2} mol dm^{-3}) with ($Na^+ \subset$ PHDB18C6)I^- (0.481×10^{-2} mol dm^{-3}) in chlorobenzene, at 60 °C.

Results

Kinetic determinations were carried out by reacting comparable amounts of phosphate esters **1**–**4** ($0.2–1.3 \times 10^{-2}$ mol dm^{-3}) and preformed ($M^+ \subset$ Lig) I^- complex ($0.1–0.6 \times 10^{-2}$ mol dm^{-3}) in the appropriate organic solvent (chlorobenzene or 1,2-dichlorobenzene) at 60 °C [reaction (1)].

Rates have been measured by potentiometric titration of the complexed nucleophile I^-. Under these conditions the reactions follow regular second-order kinetics [eqn. (2)] up to at least two half-lives (Fig. 1).

For sake of comparison the phosphate ester **1** was treated with comparable amounts of a non-complexable quaternary onium salt such as tetrahexylammonium iodide, in chlorobenzene and 1,2-dichlorobenzene. As expected, the reaction (1) is slower in both solvents and the corresponding rate constants

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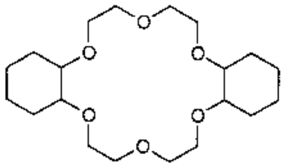
Table 1 Second-order rate constants for the demethylation reaction of **1** by $(\text{M}^+ \subset \text{Lig})\text{I}^-$ complexes and tetrahexylammonium iodide (Q^+I^-) in chlorobenzene, at 60 °C

		k^b/dm^3 mol^{-1} s^{-1}			
Cation	(z/r)/Å^{-1}	Q^+	$(\text{M}^+ \subset \text{PHDB18C6})$	$(\text{M}^+ \subset \text{PEG400Me}_2)$	$(\text{M}^+ \subset [2.2.2,\text{C}_{10}])$
Hexyl_4N^+	0.23	0.0075			
Hexyl_4N^+	0.23	0.0050^c			
NH_4^+	0.69		0.016	0.0098	0.0184
K^+	0.75		0.022	0.013	0.0179
Na^+	1.02		0.11	0.048	0.0181
Li^+	1.28		0.53	0.67	0.0180

^{a} A chlorobenzene solution (20–40 cm^3) of substrate **1** (0.5–2 × 10^{-2} mol dm^{-3}) and of the $(\text{M}^+ \subset \text{Lig})\text{I}^-$ complex or Q^+I^- (0.2–2 × 10^{-2} mol dm^{-3}). ^{b} Average of at least two determinations. The error in these values is estimated to be 5%. ^{c} Rate constant value in 1,2-dichlorobenzene.

$$\underset{\textbf{1-4}}{(4\text{-X-C}_6\text{H}_4\text{O})_2\text{P(O)OCH}_3} + (\text{M}^+ \subset \text{Lig})\text{I} \xrightarrow{\text{solv.}} (\text{M}^+ \subset \text{Lig})(4\text{-X-C}_6\text{H}_4\text{O})_2\text{P(O)O}^- + \text{CH}_3\text{I} \qquad (1)$$

X = H (**1**), CH_3 (**2**), Cl (**3**), NO_2 (**4**)
$\text{M}^+ = \text{Li}^+, \text{Na}^+, \text{K}^+, \text{NH}_4^+$
Lig = PHDB 18-crown-6 (**5**); PEG400Me_2 (**6**); $[2.2.2, \text{C}_{10}]$ (**7**)
Solvent = chlorobenzene; 1,2-dichlorobenzene



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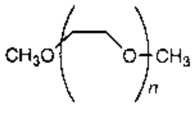

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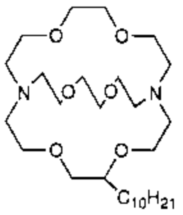

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$$\text{rate} = k\,[\text{substrate}]\,[\text{complexed I}^-] \qquad (2)$$

are lower than the slowest catalysed reactions. Results are reported in Tables 1 and 2. As shown in Table 1, the second-order rate constants k (dm^3 mol^{-1} s^{-1}) of demethylation of **1** catalysed by the complexes of crown ether **5** and PEG400-Me_2 **6** remarkably depend on the cation, increasing in the order $\text{NH}_4^+ < \text{K}^+ < \text{Na}^+ < \text{Li}^+$, whereas they are lower and independent of the cation with the complexes of cryptand **7**.

The effect of substituents [X = H (**1**); CH_3 (**2**); Cl (**3**); NO_2 (**4**)] on the rate constant k (dm^3 mol^{-1} s^{-1}) of the reaction (1) was studied by reacting the series of methyl di(*para*-substituted phenyl)phosphates **1**–**4** with the complexes of ligands **5**–**7** with the alkali metal iodides M^+I^- ($\text{M}^+ = \text{Li}^+$, Na^+ and K^+) in anhydrous chlorobenzene, at 60 °C. Reaction rates are favored by electron-withdrawing substituents with ρ values that markedly change depending on the metal ion charge and the topology of the ligand (Table 2 and Fig. 2).

Table 2 Second-order rate constants for the demethylation reaction of **1**–**4** by complexes $(\text{M}^+ \subset \text{Lig})\text{I}^-$ ($\text{M}^+ = \text{Li}^+, \text{Na}^+, \text{K}^+$) (Lig = PEG400Me_2 **6**, $[2.2.2,\text{C}_{10}]$ **7**) in chlorobenzene, at 60 °C

			k^b/dm^3 mol^{-1} s^{-1}			
			$\text{M}^+ \subset \text{PEG400Me}_2$			
	X	σ_p	Li^+	Na^+	K^+	$\text{M}^+ \subset [2.2.2,\text{C}_{10}]$
4	NO_2	0.81	10.6	1.89	1.80	3.12^c
3	Cl	0.24	1.02	0.16	0.077	0.114^c
1	H	0.0	0.67	0.048	0.013	0.018^c
2	CH_3	−0.14	0.495	0.024	0.0086	0.0089^c

^{a} A chlorobenzene solution (20–60 cm^3) of substrate **1**–**4** (0.2–2 × 10^{-2} mol dm^{-3}) and of the $(\text{M}^+ \subset \text{Lig})\text{I}^-$ complex (0.1–2 × 10^{-2} mol dm^{-3}). ^{b} Average of at least two determinations. The error in these values is estimated to be 5%. ^{c} Average rate constant value for $\text{M}^+ = \text{Li}^+$, Na^+, K^+ (see Table 1 for **1**).

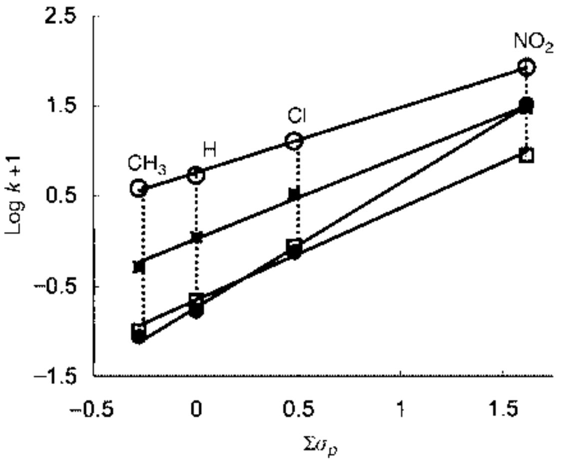


Fig. 2 Hammett correlation for the demethylation reaction of phosphate esters **1**–**4** by complexes $(\text{M}^+ \subset \text{PEG400Me}_2$, **6**$)\text{I}^-$, $\text{M}^+ = \text{Li}^+$ (○), Na^+ (■), K^+ (□), and $(\text{M}^+ \subset [2.2.2,\text{C}_{10}]$, **7**) (●), in chlorobenzene, at 60 °C.

Discussion

Results provide strong evidence of metal ion assistance ("electrophilic catalysis") in the demethylation of methyl diarylphosphates **1**–**4** promoted by complexes of ligands **5**–**7** with alkali metal iodides. The findings can be rationalized by assuming a transition state where the metal ion M^+ complexed by the ligand, $(\text{M}^+ \subset \text{Lig})$, can interact with the ion-paired anion I^- and, at the same time, with the leaving group $(\text{ArO})_2\text{PO}_2^-$ (Scheme 1).

In the activation process the $(\text{M}^+ \subset \text{Lig})\text{I}^-$ ion pair reacts following a concerted "push–pull" mechanism where the complexed metal ion stabilizes the developing negative charge on the phosphoric oxygens while favoring the simultaneous nucleophilic attack of the iodide at the methyl carbon ("electrophilic catalysis"). We have recently proposed an analogous mechanism in dealkylation reactions of phosphinic esters by complexes of metal salts with polyether ligands.[5] The higher the

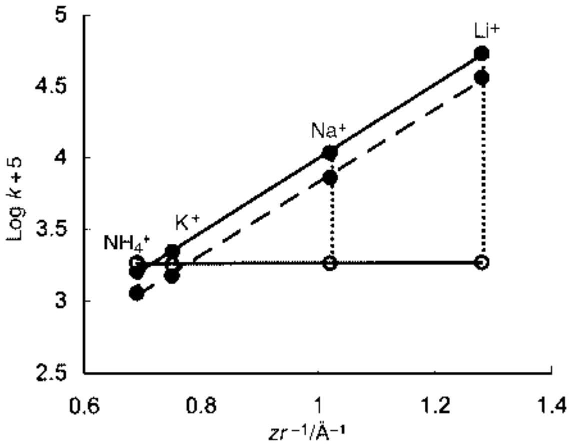
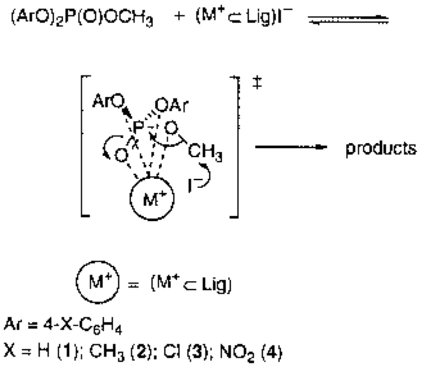


Fig. 3 Correlation between second-order rate constant k/dm^3 mol^{-1} s^{-1} and cation charge density (z/r)/Å^{-1} in the demethylation reaction of **1** by complexes ($M^+ \subset$ Lig)I^- (M^+ = NH_4^+, K^+, Na^+, Li^+) (Lig = PHDB18C6 **5** (●), [2.2.2, C_{10}] **7** (○)), in chlorobenzene (—) and 1,2-dichlorobenzene (---), at 60 °C.



Scheme 1

interaction of the complexed cation ($M^+ \subset$ Lig) with the leaving group the higher must be the reactivity of the iodide and hence the higher the corresponding rate of demethylation.

As shown in Table 1, the rate constant k (dm^3 mol^{-1} s^{-1}) of the demethylation of $(PhO)_2P(O)OMe$ **1** catalysed by the complexes of crown ether PHDB18-crown-6 **5** and polyethylene glycol PEG400Me$_2$ **6** with the series of the alkali metal iodides increases 24 and 52 times respectively on switching from KI to the corresponding complex with the lithium salt. The reactivity sequence so obtained, in the order $k_{K^+} < k_{Na^+} < k_{Li^+}$, is in line with the increasing interaction of M^+ with the leaving group on increasing the Lewis acid character of the cation ($K^+ < Na^+ < Li^+$).[10] Remarkably, this trend parallels that previously observed in the demethylation of the corresponding methyl diphenylphosphinate $Ph_2P(O)OMe$ under identical conditions ($k_{K^+} < k_{Na^+} < k_{Li^+}$).[5]

The electrophilic catalysis is also proved by the excellent linear correlation found by plotting the rate constant k (dm^3 mol^{-1} s^{-1}) as a function of the charge density of the cation, defined as M^+ charge *vs.* ionic radius ratio, for the series MI (M = NH$_4$, K, Na, Li) (Fig. 3 and Table 1). In addition, the sequence of reactivity, unchanged on going from chlorobenzene to 1,2-dichlorobenzene, does not reveal any significant modification of the transition state with the polarity of the medium. The cation being the same, the trend found $k_{\text{chlorobenzene}} > k_{\text{1,2-dichlorobenzene}}$ simply reflects the decreasing nucleophilic reactivity of the anion on increasing the solvent polarity (Fig. 3).[11]

As reported in Table 1, the enhancement of reactivity is up to about 90 times if the comparison is extended to the quaternary onium salt Hexyl$_4$N$^+$I$^-$ for which no electrophilic assistance is expected. Such enhancement could be still higher if the absence of catalysis was not compensated in part by the increased nucleophilicity of the iodide ion-paired with the bulky quaternary cation Hexyl$_4$N$^+$.[2d,e] Metal ion participation is confirmed by the lower rate constant values obtained with the complexes of cryptand **7** (Table 1). Since cryptands are known to be excellent cation complexing agents, and hence powerful anion activators, the lower reactivity found, up to about 40 fold, is another additional proof of cation electrophilic assistance to reaction (1).

The study of the effect of the *para* substituents X on the demethylation rate of phosphate esters **1**–**4** has revealed that, the complex ($M^+ \subset$ Lig) I^- being the same, the second-order rate constants k (dm^3 mol^{-1} s^{-1}) are linearly related with the corresponding Hammett σ_p-values.[12] Reactions are favored by electron-withdrawing groups, that stabilize the developing negative charge on the phosphoric oxygens (Scheme 1), with ρ values ranging from 0.7 up to 1.38, depending on both the metal cation (Li^+, Na^+, K^+) and the ligand (**5**–**7**) (Table 2, Fig. 2).

Interestingly, as shown in Fig. 2 for the complexes ($M^+ \subset$ PEG400Me$_2$)I^-, the ρ values increase, in the order $Li^+ < Na^+ < K^+$, revealing a different sensitivity of the reaction (1) to the effects of the substituent X on changing the cation M^+. These data can be rationalized in terms of a different involvement of metal ion and substituent in the activation process (Table 2). With a cation of high density of charge like lithium the electrophilic catalysis of the metal ion is most likely the dominant effect and hence the reaction is scarcely affected by the electronic effects of the substituent (ρ = 0.71). By contrast, with cations of lower charge density ($Na^+ > K^+$) the prevailing effect becomes that of the substituent and the ρ values increase in the same order [ρ = 0.99 (Na^+); ρ = 1.25 (K^+)]. This hypothesis is also confirmed by the similar value (ρ = 1.38) obtained with the complexes of cryptand [2.2.2,C$_{10}$] **7** where the cation, completely included into the cavity of the tridimensional ligand, cannot assist the departure of the leaving group in the transition state (Scheme 1).

A very similar result (ρ = 1.1) was reported by Osborne in reactions of methyl di(*para*-substituted phenyl)phosphates with pyridine to give the corresponding *N*-methylpyridinium phosphates.[13]

Conclusions

The data as a whole reveal metal ion participation ("electrophilic catalysis") in the demethylation reaction of methyl diarylphosphates **1**–**4** promoted by complexes of polyethers **5**–**7** with alkali metal iodides in low polarity media. The catalytic effect depends on the Lewis acid character of the cation, increasing in the order $K^+ < Na^+ < Li^+$, as well as on the ability of the ligand to effectively shield the metal ion charge.

Kinetic results show a different sensitivity (different Hammett ρ values) of the reaction to the substituent effects on changing the cation M^+. Whereas metal ion catalysis is the dominant effect with the high charge lithium, the substituent effect progressively increases with cations of lower charge density (sodium and potassium) and prevails whatever the cation may be with a better complexing agent like cryptand **7**.

Experimental

General methods

Potentiometric titrations were carried out with a Metrohm 670 Titroprocessor by using a combined silver electrode isolated with a potassium nitrate bridge. Karl–Fischer determinations were performed with a Metrohm 684KF coulometer. ^{1}H and ^{31}P NMR spectra were recorded on Bruker AC 300 and AMX 300 spectrometers, using as external references TMS and aqueous 85% H_3PO_4, respectively.

Materials and solvents

Tetrahexylammonium iodide, ligands PHDB18-crown-6 **5** and PEG400Me$_2$ **6** and [2.2.2,C$_{10}$] **7** were commercial products, utilized as purchased. Alkali metal and ammonium iodides, AnalaR grade commercial products, were first ground then dehydrated in an oven at 110–120 °C under vacuum for several hours. In all cases the water content is ≤ 0.05 mol of H_2O per mol of salt (Karl Fischer titration). Dry (Fluka) chlorobenzene and 1,2-dichlorobenzene ($H_2O \leq 15$ ppm) were used.

Synthesis of methyl di(*para*-substituted)phosphates **1**–**4** will be published elsewhere.[14]

Kinetic measurements

In a typical procedure a standardized solution (5–15 cm^3) of substrate **1**–**4** (0.02–0.05 M) was added to a standardized solution (15–45 cm^3) of preformed complex or tetrahexylammonium iodide (0.0028–0.050 mol dm^{-3}) in a 100 cm^3 flask kept at 60 ± 0.1 °C. Samples (2–15 cm^3), withdrawn periodically, were quenched in ice-cold MeOH (50 cm^3), and the unreacted nucleophile I$^-$ was potentiometrically titrated with 0.01 M $AgNO_3$. The second-order rate constants were evaluated using a least-squares computer program (Excel program) from the equation $1/([B]_0 - [A]_0)\ln ([B][A]_0/[A][B]_0) = kt$, where A = substrate and B = complexed MI (or tetrahexylammonium iodide) or *vice versa*. All rates involved at least eight samplings and gave correlation coefficients of 0.997 or better.

The solutions of the preformed complexes of **5** and **7** were prepared by magnetically stirring a standardised solution (20–50 cm^3) of ligand in the organic solvent (chlorobenzene, 1,2-dichlorobenzene) (0.009–0.010 mol dm^{-3}) with the appropriate quantity of salt MI (0.7–0.9 mol per mol of ligand) as a solid phase in a flask thermostatted at 60 ± 0.1 °C. The system was stirred for 1–3 h and then kept without stirring for an additional 10 min to allow good separation of the two phases. Aliquots (5–8 cm^3) of the organic phase were centrifuged and samples (2–4 cm^3) were withdrawn and titrated with 0.01 M $AgNO_3$. Potentiometric titrations of cryptates ($M^+ \subset [2.2.2,C_{10}])I^-$ were performed in acid medium (HNO_3) in order to avoid the simultaneous titration of the free ligand.[2a]

The fastest kinetics were performed by using the "quenching" technique. In a typical procedure standardized solutions (3 cm^3) of substrate (0.01045 mol dm^{-3}) were added with standardized solutions (27 cm^3) of preformed complex (0.00225 mol dm^{-3}) in a series (7–10) of 50 cm^3 flasks kept at 60 ± 0.1 °C. At different times the reactions were quenched in ice-cold MeOH (50 cm^3) and the unreacted iodide potentiometrically titrated with 0.01 mol dm^{-3} $AgNO_3$.

Reaction products

The products of reaction (1) were isolated as solid salts from the crude mixture and identified by ^{1}H and ^{31}P NMR. The spectroscopic analysis showed the exclusive formation of the demethylation products $(4\text{-}XC_6H_4O)_2P(O)O^-M^+$ (X = H, CH_3, Cl, NO_2; $M^+ = Li^+, Na^+, K^+$) in all cases. Indeed, the ^{31}P NMR spectra (D_2O) showed only a singlet centred at $\delta - 7.8$ to -8.1 ppm and the ^{1}H NMR spectra (D_2O) confirmed the absence of the methoxy group. In particular, they are as follows: $(C_6H_5O)_2P(O)O^-M^+$, ^{31}P NMR, δ −8.13 (s); ^{1}H NMR, δ 7.38 (m). $(4\text{-}CH_3C_6H_4O)_2P(O)O^-M^+$, ^{31}P NMR, δ −7.80 (s); ^{1}H NMR, δ 7.12 (dd, 8H, J 8.48), δ 2.2 (s, 6H). $(4\text{-}ClC_6H_4O)_2P(O)O^-M^+$, ^{31}P NMR, δ −8.01 (s); ^{1}H NMR, δ 7.10 (dd, J 7). $(4\text{-}NO_2C_6H_4O)_2P(O)O^-M^+$, ^{31}P NMR, δ −8.10 (s); ^{1}H NMR, δ 7.81 (dd, J 9.17).

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