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Highly concentrated 1,2-bis(perfluoroalkyl)iodoethene emulsions for use as contrast agents for diagnosis

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Abstract

New 1,2-bis(*F*-alkyl)-1-iodoethenes, $C_nF_{2n+1}CH{=}CIC_{n'}F_{2n'+1}$ (F*nn*′IE), have been evaluated as to their emulsifying ability for use as contrast agents. Highly concentrated (up to 90% w/v), heat-sterilizable emulsions were obtained with egg yolk phospholipids (EYP) as surfactant, with both small average particle sizes and narrow size distributions. The emulsions prepared from F*nn*′IE with $n+n'=10$ were more stable at 40 °C than those with $n+n'=8$. The latter were stabilized by replacing a small amount ($\sim 3\%$ w/v) of F*nn*′IE by an iodinated mixed hydrocarbon/fluorocarbon molecule $C_nF_{2n+1}CH{=}CIC_mH_{2m+1}$ (F*n*H*m*IE) acting as a molecular dowel, without any adverse consequence on the radiopacity. Phase separation occurred, however, in all cases after about two months at 40 °C. The in vitro radiopacity of these emulsions is, for the same concentration, three- to four-times larger than that of perfluoro-octyl bromide. However, a decrease in pH during heat-sterilization and upon ageing, which compromised their use in vivo, was observed.

Keywords: Emulsions; Contrast agents; Bis(perfluoroalkyl)iodoethene; Surfactants; Radiopacity

1. Introduction

In contrast to numerous well-tolerated water-soluble contrast agents, few lipidic radiopaque compounds have been developed, despite their interesting specific properties [1]. For example, unlike water-soluble contrast media, their emulsions do not diffuse into interstitial spaces; hence they produce prolonged contrast, and the emulsion clearance from the vascular system by phagocytosis makes them ideal for imaging the hepatic system [2]. Recent investigations in this field have singled out perfluoro-octyl bromide (Perflubron, PFOB) as an outstanding candidate for radiopaque media [3]. Because of their biological and chemical inertness and high oxygen dissolving capacity, perfluorocarbons are being evaluated in various applications in medicine, and especially, when emulsified, as in vivo oxygen carriers (so-called 'blood substitutes') [4]. However, perfluorocarbons are also valuable in diagnosis, including ultrasound imaging, proton magnetic resonance imaging (MRI) and fluorine MRI [3]. PFOB, which has one bromine atom, also has potential in computed X-ray tomography [5]. The bromine atom has, however, a lower radiopaque effect than iodine [6], but perfluoroalkyl iodides, obviously the simplest possible PFOB substitutes, have to be avoided because of their high chemical reactivity in radical reactions [7]. This is why the design and synthesis of new families of biocompatible iodinated fluorocarbons with higher efficiency in radiopacity and lower reactivity and toxicity than perfluoroalkyl iodides is a challenge for chemists.

A preliminary study led us to select 1,2-bis(*F*-alkyl)-iodoethenes ($C_nF_{2n+1}CH{=}CIC_{n'}F_{2n'+1}$, so-called F*nn*′IE) as candidates as contrast agents for diagnosis. These compounds were chosen for their absence of toxicity when administered intraperitoneally in mice, molecular weight, thermal stability, capacity to be emulsified and high radiopacity [8]. We report here the emulsification properties of these compounds, and describe the decrease in pH which occurs during heat-sterilization of these emulsions.

2. Experimental details

2.1. Materials

The 1,2-bis(*F*-alkyl)iodoethenes (F*nn*′IE, $Z/E \sim 95{:}5$) and 1-alkyl-2-(*F*-alkyl)-1-iodoethenes ($C_nF_{2n+1}CH{=}CIC_mH_{2m+1}$, F*n*H*m*IE, $Z/E \sim 90{:}10$) used in this study were synthesized via the radical addition of *F*-alkyl iodides (R_FI) on appropriate alkynes [7–9]. Each batch of these iodofluorocarbons utilized was detoxified as previously described

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[10], and displayed a better than 99% grade of purity (GLC).

PFOB was obtained from Hoechst (Corpus Christi, USA) and egg yolk phospholipids (EYP) from Lipoid KG (Ludwigshafen, Germany). The phosphate buffer blend for 1 l of water contained 5.50 g of NaCl (94 mmol), 0.39 g of $Na_2EDTA \cdot 2H_2O$ (1 mmol), 1.15 g of $NaH_2PO_4 \cdot 2H_2O$ (7.4 mmol), 9.31 g of $NaHPO_4 \cdot 12H_2O$ (26 mmol) and 0.04 g of α-tocopherol (0.09 mmol). At the end of the preparation, the pH was adjusted using a 1 N solution of NaOH. The tris(hydroxymethyl)aminomethane (TRIS) buffer preparation was obtained by dissolving 6.61 g and 0.97 g of Trizma HCl and Trizma base salts (Sigma), respectively, in 1 l of water, producing 0.05 M TRIS/HCl solution, pH = 7.4 at 25 °C. Water for injectable preparations was used in all the experiments.

2.2. General methods

Emulsification of fluorocarbons was achieved by microfluidization (Microfluidics model M110F). The average particle sizes (μm ± 10%) and particle size distributions were measured with a Horiba Capa 700 Analyser based on light absorption during centrifugal sedimentation. To overcome the difficulties in particle size measurement due to the very low difference in refractive index between F*nn*′IE compounds (1.3362–1.3392) [8] and water (1.333), analyses were performed on emulsion samples diluted with a 30% aqueous sucrose solution which increased this difference. The viscosity of the emulsions was measured at room temperature on a Rheo viscometer model LV8. The X-ray contrast was measured on a Philips Tomoscan LX apparatus (120 kV, 175 mA) with samples of emulsions diluted five times in water.

2.3. Preparation by microfluidization of 50/2.5 (90/4)% w/v PFOB or Fnn′IE/EYP emulsions

Preparation of 30 ml samples of fluorocarbon/EYP emulsion was carried out under nitrogen. Thus, 0.75 g for 50/2.5% emulsions (1.2 g for 90/4% emulsions) of EYP were dispersed at 4 °C in ~21.6 (~14.9) ml of buffered water with an Ultra-Turrax homogenizer (model T-25, rotor 25F) for 1 min at 8000 rpm. Then 15 (27) g of fluorocarbon were added dropwise at the rate of 20 ml s^{-1}. After 10 min of mixing at 24000 rpm, this pre-emulsion was immediately run through the microfluidizer at 30 °C. The number of passes was 12 for all the preparations.

2.4. Preparation by microfluidization of (90 − x/x/4)% w/v F44IE/FnHmIE/EYP emulsions (x = 3 and 3.6 for F6H6IE and F8H6IE, respectively)

The emulsions were prepared as above, the sequence of fluorocarbon addition being first F*n*H*m*IE, then F44IE. The quantity *x* was calculated in order to obtain an F*n*H*m*IE/EYP molar ratio of 1:1, considering an average molecular weight of 730 for EYP.

2.5. Sterilization and ageing of the emulsions

The emulsions were divided into 5 ml aliquots and bottled in 6 ml sealed flasks sparged with argon. They were sterilized in an oscillating autoclave at 121 °C for 15 min, or filtered through Anotop 25 Plus filter (0.2 μm). The emulsions were stored at 4, 25 and 40 °C, the latter temperature allowing a significant acceleration of the ageing process. Particle size and size distribution measurements were carried out immediately after preparation, after sterilization and at increasing time intervals over three months.

2.6. Biocompatibility

A group of 10 SPF OFA Sprague Dawley rats (ca. 200 g) were injected intravenously with the emulsion at a 2.5 ml kg^{-1} bw dose. Mortality and signs of toxicity were observed over 30 d.

3. Results and discussion

In addition to having high contrast capacity and being well-defined compounds with a high level of purity, reproducibility and industrial feasibility, fluorocarbons destined to serve as contrast agents in diagnosis have to provide stable, biocompatible emulsions with high intravascular persistence and low retention time in organs. In view of these requirements and on the basis of preliminary physicochemical and biological tests [8], five iodofluorocarbons F*nn*′IE were selected for further evaluation. The fluorocarbons chosen can be divided into two groups according to their molecular weight (MW): 590 (F26IE and F44IE) and 690 (F28IE, F46IE and F64IE) for the $n+n'=8$ series (MW = 590) and $n+n'=10$ series (MW = 690), respectively. This difference, independent of other factors, has a priori consequences in the excretion of the compounds from organs, their radiopaque effect and their emulsion stability [11]. For injectable applications, it was shown that the excretion rate of fluorocarbons is not only dependent on their MW (the heavier, the more retained) but also on their lipophilicity [4,12]. Thus, we undertook the evaluation of fluorocarbons made lipophilic by an iodine atom [12], which were also expected to have a shorter retention time than could be foreseen on the bases of their MW alone. Since medium concentrated emulsions (F*nn*′IE/EYP, 50/2.5% w/v) investigated in preliminary studies showed no notable differences (particle size and size distribution after preparation, after sterilization and during ageing) in comparison with the more highly concentrated ones, the following discussion will describe only 90% w/v F*nn*′IE emulsions.

To investigate F*nn*′IE emulsion stability and radiopacity, we chose the formulation which was optimized for PFOB, a presently developed, highly effective second generation emulsion for in vivo oxygen delivery. The 90% w/v (47% v/v) of PFOB formulation with 4% EYP as surfactant in a phosphate buffer represents an optimum compromise between O_2 dissolving capacity or radiopacity and emulsion fluidity.

3.1. Emulsification properties

3.1.1. Emulsion aspect and temperature effect

Preliminary emulsification tests showed that all F*nn*′IE were emulsifiable for concentrations up to 90% w/v with natural egg yolk phospholipids (EYP). During the emulsification process, right from the first run through the microfluidizer, F*nn*′IE emulsions were more transparent in comparison with those of PFOB. This is explained by the low difference in refractive indices (0.003–0.006) between water and F*nn*′IE [8] compared to water and PFOB.

The evolution of the average droplet sizes in the 90/4% w/v iodofluorocarbon/EYP emulsions after preparation, sterilization and over time for four months at 4 °C and 25 °C are shown in Table 1. A PFOB emulsion was chosen as a reference. All the F*nn*′IE materials gave fine emulsions after preparation with similar average particle sizes, from 0.06 to 0.10 μm with narrow droplet size distributions. These emulsions withstood heat-sterilization conditions, their average particle size increasing, however, by 10%–50% during the process.

After four months, no differences in behaviour appeared for ageing at 4 °C or 25 °C; the average particle growth was still only of 1–1.4-fold, comparable to 1.5-fold for the reference emulsion. The rate of enlargement seems to depend to a slight extent on molecular weight. In order to accelerate the ageing process and shorten the time needed for evaluation, further investigations were effected at 40 °C.

3.1.2. Effect of the compound emulsified

To investigate the impact of the nature of halofluorocarbons on emulsion stability, highly concentrated (90% w/v) sterilized emulsions of F*nn*′IE were prepared with a phosphate buffer (0.032 M) and monitored at 40 °C. Fig. 1 illustrates the ageing of these emulsions. A definitely higher stability was found for emulsions of iodinated fluorocarbons of higher molecular weight, i.e. for compounds with $n+n'=10$ compared to those with $n+n'=8$. For the $n+n'=10$ series, no significant change in median diameter and in size distribution was observed over a three month period at 40 °C, irrespective of the products tested (F28IE, F46IE, F64IE). The average growth rate, defined as J_{100}/J_0, for these series was about 1.3 in comparison with 2.5 for PFOB. For F*nn*′IE with $n+n'=8$, the average particle diameter after two months at 40 °C increased from 0.13 to 0.18 μm ($J_{60}/J_0=1.4$) and 0.09 to 0.35 μm ($J_{60}/J_0=3.9$) for F26IE and F44IE, respectively, while the PFOB emulsion grew from 0.10 to 0.23 μm ($J_{60}/J_0=2.3$). This behaviour is in agreement with previous studies showing that, for example, for emulsions of 1,2-bis-(*F*-alkyl)ethenes (F*nn*′E) prepared with Pluronic F-68, the stability of the emulsion increases with the molecular weight of the fluorocarbon [13].

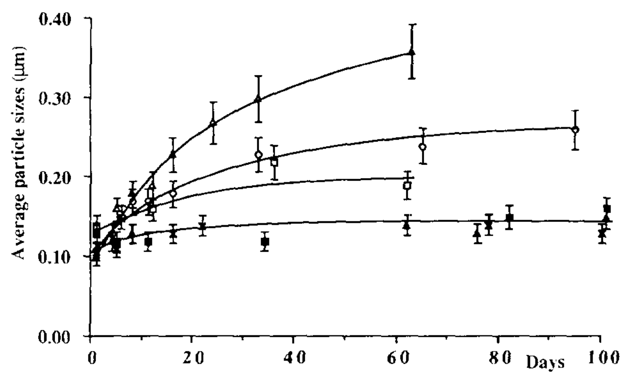

Fig. 1. Evolution over time of the average particle sizes of sterilized 90% w/v emulsions, prepared in phosphate buffer, with 4% w/v EYP for various F*nn*′IE fluorocarbons [$n+n'=10$, F28IE (▲), F46IE (×), F64IE (■); and $n+n'=8$, F26IE (□), F44 IE (△)] compared to PFOB (○) reference.

The F26IE emulsion was more stable than that of F44IE. This difference probably results from the fact that F26IE contained a low proportion (≤1%, GLC monitoring) of the superior homologue, F46IE [8]. It is well known that emulsions can be stabilized by adding a small amount of a significantly heavier MW fluorocarbon [14]. The stabilizing effect is directly related to the solubility and diffusibility of the additive in the aqueous phase, which, within a homologous series, is related to molecular weight [15].

Whatever the fluorocarbon concentration (50% or 90%), all the emulsions of the $n+n'=8$ series prepared as indicated above rapidly broke down after two months at 40 °C, whereas the $n+n'=10$ series remained intact during the three or four months observation period. However, when F26IE was emul-

Table 1
Evolution over time of the average particle size (μm ± 10%) of 90% (w/v) halofluorocarbon emulsions prepared in phosphate buffer with 4% (w/v) EYP

Compound	After preparation	After sterilization	After 4 months at 4 °C	After 4 months at 25 °C	Ratio J_{120}/J_0 [a]
PFOB	0.09	0.10	0.14	0.15	1.5
F26IE	0.10	0.13	0.17	0.17	1.3
F44IE	0.07	0.09	0.13	0.13	1.4
F28IE	0.09	0.10	0.10	0.10	1.0
F46IE	0.06	0.09	–	–	–
F64IE	0.09	0.13	0.15	0.14	1.1

[a] J_0 and J_{120}: average particle size after sterilization and after 120 d, respectively.

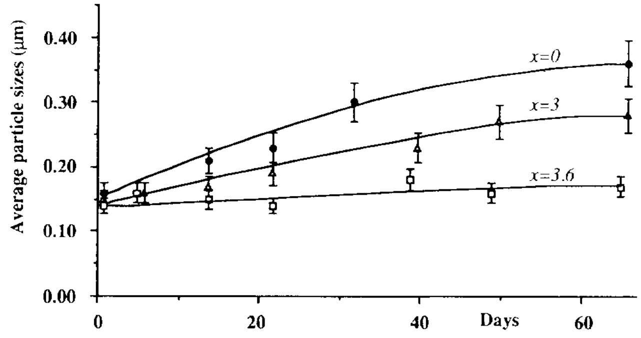

Fig. 2. Stabilization of sterilized concentrated F44IE/EYP emulsions by molecular radiopaque dowels FnHmIR (x), prepared in TRIS buffer; formulation F44IE/FnHmIE/EYP, 90 − x/x/4% w/v [$x=3$ for F6H6IE (△), $x=3.6$ for F8H6IE (□)].

sified (90% w/v) with a more concentrated phosphate buffer, 0.064 M instead of 0.032 M, the emulsion was preserved from phase separation for over five months at 40 °C.

3.1.3. Stabilizing effect of FnHmIE compounds on F44IE emulsions

Among the compounds studied, F26IE and F44IE ($n+n'=8$ series) have two advantages: their lower MW which is expected to result in faster excretion rate from organs [11] and, for a same (w/v) emulsion concentration in fluorocarbon, a higher molar concentration and hence a higher radiopacity. Since the emulsions of these compounds, especially F44IE, were less stable than their analogues of the $n+n'=10$ series, a means was sought to stabilize them. One of the most effective ways to improve the stability of fluorocarbon emulsions is to incorporate perfluoroalkylated amphiphiles [16] and especially mixed fluorocarbon/hydrocarbon compounds of the R_FR_H type, the so-called molecular dowels [17–19].

To retain the maximum radiopaque capacity of F*nn*′IE emulsions, we chose to evaluate as stabilizers two iodinated additives of the 1-alkyl-2-(*F*-alkyl)-1-iodoethene type, F6H6IE ($C_6F_{13}CH{=}CIC_6H_{13}$) and ($C_8F_{17}CH{=}CIC_6H_{13}$) whose biocompatibility appears to be acceptable (~45 g kg^{-1} body weight, mice, intraperitoneal injection) [20].

To this end, we studied emulsions in TRIS buffer (0.05 M, pH = 7.4 at 25 °C) with 4% (w/v) of EYP and 90% (w/v) of a mixture of F44IE and F*n*H*m*IE in which the amount of F*n*H*m*IE was equimolar to that of the lecithins. F44IE/F*n*H*m*IE/EYP (90 − x/x/4% w/v) preparations with $x=0$ (reference emulsion), $x=3$ (F6H6IE) and $x=3.6$ (F8H6IE) were investigated. The incorporation of F*n*H*m*IE in F44IE emulsions did not modify significantly the distribution and average particle size after preparation and sterilization. No change was observed after two months at 40 °C for the emulsion prepared with F8H6IE.

The three formulations had the same 0.13–0.15 μm mean diameter after sterilization but displayed different behaviour upon ageing at 40 °C (Fig. 2). Emulsions prepared with F*n*H*m*IE additives, in particular with F8H6IE, were more stable than the F44IE reference emulsion. Thus, these iodinated amphiphiles (F*n*H*m*IE) have similar stabilizing properties to those of the 1-(*F*-alkyl)-2-alkylethene (F*n*H*m*E) [17,18]. After 60 d at 40 °C, the average particle sizes are still only 1.2-fold larger for the emulsion incorporating F8H6IE, compared to 2.3-fold for the reference emulsion; the emulsion with F6H6IE as an additive had an intermediate behaviour (1.9-fold) (Table 2).

However the effect of F*n*H*m*IE, even in the case of F8H6IE, on F44IE emulsions, was not sufficient to avoid phase separation after two months ageing.

3.1.4. Variation of emulsion pH during sterilization

Monitoring of the pH during the whole emulsification process showed a decrease in pH for emulsions prepared in the phosphate buffer (0.32 M) during thermal sterilization. Analyses of sterilized emulsions, by means of GLC and ^{19}F NMR spectroscopy, gave, however, no indication of the formation of new products.

The buffer and its concentration were chosen as it fitted well for PFOB emulsions, whose pH slightly decreased from 7.4 to 7.2 during sterilization but stayed physiologically acceptable. For a similar formulation, the pH of F*nn*′IE emulsions decreased from 7.3–7.4 (initial values) to pH ~ 5.9 for the $n+n'=8$ and ~6.5 for the $n+n'=10$ series. It was possible to delay phase separation somewhat by increasing the buffer concentration.

The difficulties involved during the course of the thermal sterilization of iodinated lipidic or water-soluble contrast media have already been described in the literature [21]. The decrease in pH was always ascribed to the release of iodine and free acids. It was shown that some iodinated water-soluble contrast agents can be heat-sterilized without degradation in acidic medium (pH ~ 4.7) [22]. To overcome this difficulty, a TRIS buffer was chosen because of its pH versus temperature dependence: its pK_a value decreased by 0.025 unit per °C upon heating, allowing the attainment of a pH value which was better suited to the stability of iodinated contrast agents during autoclaving at 120 °C. When applied to iodofluorocarbon emulsions, this allowed the preservation of their neutrality (pH in the 7–7.2 range) after sterilization. Nevertheless, during ageing at 40 °C, the pH of the emulsions (irrespective of the compounds involved) rapidly decreased,

Table 2
Evolution over time at 40 °C of the average particle size (μm ± 10%) of F44IE/F*n*H*m*IE/EYP (90 − x/x/4% w/v) emulsions prepared in TRIS buffer

F*n*H*m*IE added	x	After preparation	After sterilization	After 2 months at 40 °C	Ratio J_{60}/J_0 [a]
	0	0.10	0.15	0.35	2.3
F6H6IE	3	0.13	0.14	0.27	1.9
F8H6IE	3.6	0.11	0.13	0.16	1.2

[a] J_0 and J_{60}: average particle size after sterilization and after 60 d, respectively.

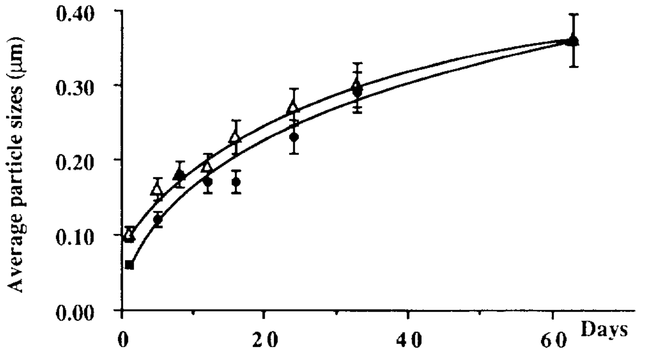

Fig. 3. Comparison of ageing at 40 °C for heat-sterilized (△) and filtered (●) F44IE/EYP emulsions (90/4% w/v) prepared in phosphate buffer.

Table 3
Radiopacity and viscosity coefficient after sterilization of halofluorocarbon emulsions

Emulsions [a]	Concentration of fluorocarbon %w/v	Radiopacity [c] (HU ± 10%)	Viscosity coefficient (mPa s, ±2%)
F44IE	90	1030	8
F26IE	90	715	
F44IE/F6H6IE	86.4/3.6	810	
F44IE/F8H6IE	87/3	850	
F44IE/F6H6IE [b]	48/2	460	
F28IE	90	600	
F46IE	90	920	13.3
F46IE [b]	50		2
F64IE	90	730	
PFOB	90	260	12.2

[a] Prepared with 4% of EYP.
[b] Prepared with 2.5% of EYP.
[c] Hounsfield unit (HU).

while phase separation occurred after two months whatever the $n+n'$ value. This behaviour is probably related to the hydrolysis of EYP, leading to acidification [23].

Sterilization by filtration which is used in liposome technology [24], but not for parenteral emulsions, was also used. An attempt was performed on an F44IE emulsion (90% w/v). Filtration did not alter significantly the particle size distribution and Fig. 3 shows that the sterilized and filtered emulsion behaved similarly upon ageing at 40 °C. This procedure needs further investigation, especially in relation to emulsion biocompatibility.

3.2. Physical and biological properties

The X-ray contrast of F*nn*'IE emulsions was evaluated in vitro for all the emulsions after five-fold dilution in water, taken as the reference (Table 3). As expected, owing to the results obtained for the neat halofluorocarbons [8], the 90% w/v F*nn*'IE emulsions were three to four times more radiopaque (~750 and ~870 HU for the $n+n'=10$ series and $n+n'=8$ series, respectively) than for PFOB (~260 HU). The contrast intensity depends on the concentration of halofluorocarbons and on its molecular weight, and remains the same for F44IE emulsions in which the iodofluorocarbon was replaced by the same amount of F6H6IE or F8H6IE.

In view of their intended intravascular use, the viscosity coefficient of the F*nn*'IE emulsions was measured and compared with that of well-documented PFOB emulsion. Table 3 shows that 90% w/v preparations of PFOB and F46IE have similar viscosity coefficients, 12.2 mPa s (cP) and 13.3 mPa s respectively, while the F44IE emulsion was less viscous (8 mPa s).

Although the neat F*nn*'IE compounds were not toxic when injected intraperitoneally at 49 g kg^{-1} body weight in mice (100% survivals after one month) [8], their intravenous tolerance in emulsified form was limited, probably because of the decrease in pH during sterilization. A 90% w/v F46IE emulsion prepared with a TRIS buffer administered immediately after sterilization at physiological pH, displayed in rats only an $LD_{50}=2.5$ ml kg^{-1} bw (i.e. 2.3 g of neat F46IE). Although this dose represents four- to five-times the dose necessary to obtain an efficient contrast in vivo [20], it is about 15-times lower than for PFOB emulsions of the same concentration.

Acknowledgments

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