^{18}F-FDG Radiosynthesis: A Landmark in the History of PET

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Virtually all of the brain's energy derives from glucose metabolism. This underpins the development of ^{18}F-FDG, a radiotracer that was first used to measure regional brain glucose utilization in humans, and has had a profound influence on research in the neurosciences (*1*). The subsequent discovery that ^{18}F-FDG can be used to assess viable myocardium and also accumulates in tumors in proportion to their degree of malignancy underpins the evolution of PET as a major clinical tool in cancer diagnosis and monitoring of treatment.

The 1986 landmark paper by Hamacher and colleagues in *JNM* represents a major milestone in the present use of ^{18}F-FDG in clinical nuclear medicine worldwide (*2*).

The ^{18}F-FDG molecule was modeled on the ^{14}C-labeled 2-deoxyglucose method, which measures regional brain glucose utilization in animals (*3*). 2-deoxyglucose is an analog of glucose in which the hydroxyl group on C-2 is replaced by a hydrogen atom. It mimics glucose in serving as a substrate for hexokinase, the rate-limiting step in glycolysis, but does not undergo further steps in the conversion of glucose to energy. Its translation to humans required the development of a radiolabeled version of the 2-deoxy-D-glucose molecule that maintained its biochemical properties and could be labeled with a radioisotope suitable for external imaging in humans. A survey of the literature at the time revealed that 2-deoxy-2-fluoro-D-glucose (in which the hydrogen atom on C-2 was replaced by a fluorine atom) met these requirements. An electrophilic reaction with ^{18}F using elemental fluorine ($[^{18}F]F_2$) produced via the ^{20}Ne(d,α)^{18}F reaction on Brookhaven's 152-cm (60-in) cyclotron (*4*) was developed and used to produce ^{18}F-FDG in sufficient yield for transport from Long Island to the University of Pennsylvania for the first human studies in 1976 (*1,5*).

Over the next 10 years, the demand for ^{18}F-FDG grew. This created the need for a simpler and higher-yield radiosynthesis that would be more amenable to automation and regional distribution. Indeed, the electrophilic radiosynthesis had shortcomings.

Received May 24, 2020; revision accepted May 28, 2020.
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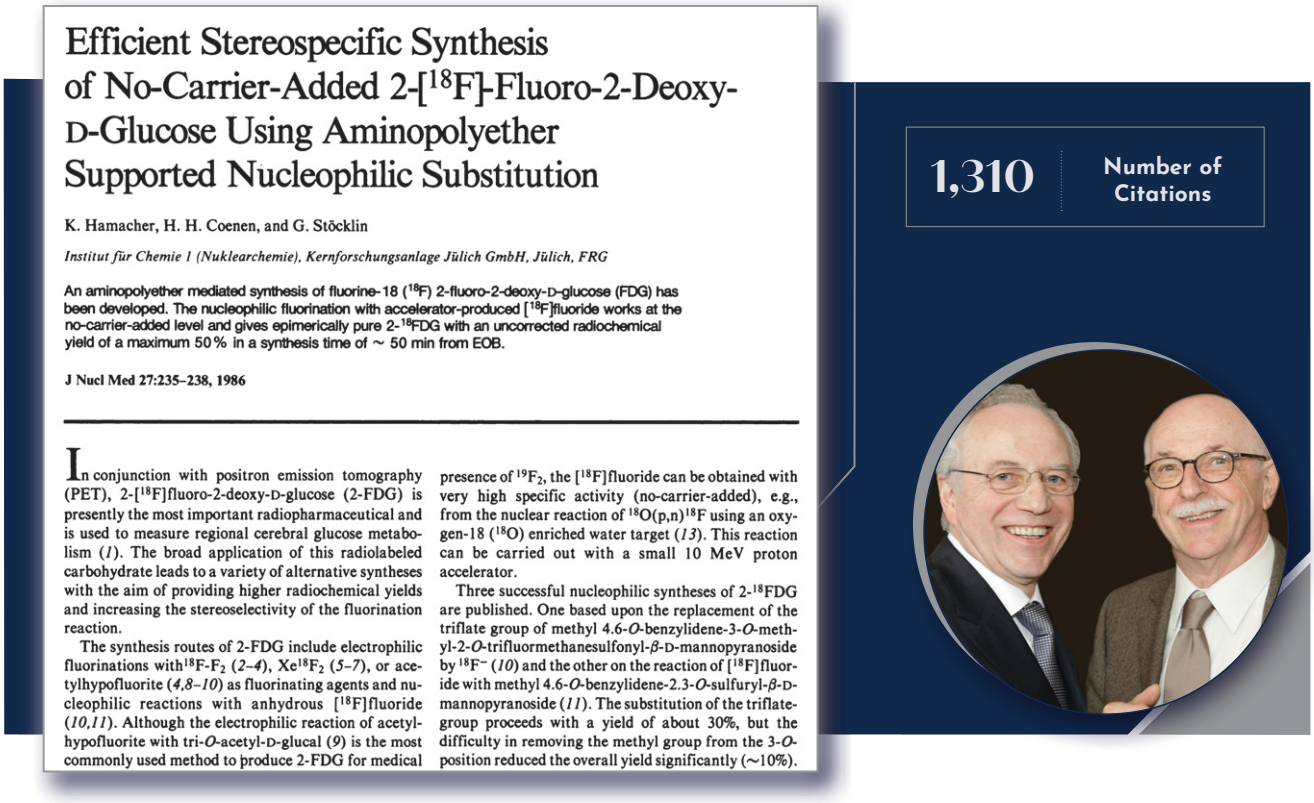
DOI: 10.2967/jnumed.120.250191



Efficient Stereospecific Synthesis of No-Carrier-Added 2-[^{18}F]-Fluoro-2-Deoxy-D-Glucose Using Aminopolyether Supported Nucleophilic Substitution

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An aminopolyether mediated synthesis of fluorine-18 (^{18}F) 2-fluoro-2-deoxy-D-glucose (FDG) has been developed. The nucleophilic fluorination with accelerator-produced [^{18}F]fluoride works at the no-carrier-added level and gives epimerically pure 2-^{18}FDG with an uncorrected radiochemical yield of a maximum 50% in a synthesis time of ~ 50 min from EOB.

J Nucl Med 27:235–238, 1986

In conjunction with positron emission tomography (PET), 2-[^{18}F]fluoro-2-deoxy-D-glucose (2-FDG) is presently the most important radiopharmaceutical and is used to measure regional cerebral glucose metabolism (*1*). The broad application of this radiolabeled carbohydrate leads to a variety of alternative syntheses with the aim of providing higher radiochemical yields and increasing the stereoselectivity of the fluorination reaction.

The synthesis routes of 2-FDG include electrophilic fluorinations with ^{18}F-F_2 (*2–4*), Xe$^{18}F_2$ (*5–7*), or acetylhypofluorite (*4,8–10*) as fluorinating agents and nucleophilic reactions with anhydrous [^{18}F]fluoride (*10,11*). Although the electrophilic reaction of acetylhypofluorite with tri-*O*-acetyl-D-glucal (*9*) is the most commonly used method to produce 2-FDG for medical presence of $^{19}F_2$, the [^{18}F]fluoride can be obtained with very high specific activity (no-carrier-added), e.g., from the nuclear reaction of ^{18}O(p,n)^{18}F using an oxygen-18 (^{18}O) enriched water target (*13*). This reaction can be carried out with a small 10 MeV proton accelerator.

Three successful nucleophilic syntheses of 2-^{18}FDG are published. One based upon the replacement of the triflate group of methyl 4.6-*O*-benzylidene-3-*O*-methyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranoside by ^{18}F$^-$ (*10*) and the other on the reaction of [^{18}F]fluoride with methyl 4.6-*O*-benzylidene-2.3-*O*-sulfuryl-β-D-mannopyranoside (*11*). The substitution of the triflate-group proceeds with a yield of about 30%, but the difficulty in removing the methyl group from the 3-*O*-position reduced the overall yield significantly (~10%).

1,310 Number of Citations

[^{18}F]F_2 production was technically complex and required the addition of highly toxic and reactive fluorine gas. With [^{18}F]F_2, only a maximum 50% of the ^{18}F produced by the ^{20}Ne(d,α)^{18}F reaction could be incorporated into the final product; this synthesis also gave a mixture of isomers, reducing the overall yield. Fortunately, ^{18}F (as fluoride ion) could also be produced in far higher yields via the ^{18}O(p,n)^{18}F reaction than via the ^{20}Ne(d,α)^{18}F reaction. Production of ^{18}F also did not require the addition of fluorine gas (*4*). This set the stage for intense competition between different groups of chemists to produce ^{18}F-FDG via a nucleophilic displacement reaction with [^{18}F]fluoride ion. Several different nucleophilic routes were explored from 1976 to 1986 (*4*). However, similar to the electrophilic route, all were plagued with difficult steps, including low yields in the incorporation of ^{18}F and difficulty in removal of protective groups.

A major advance in the synthesis of ^{18}F-FDG from [^{18}F]fluoride was reported in 1986 when Hamacher and colleagues at the Kernforschungsanlage Jüulich reported that Kryptofix [2.2.2] (Merck), a phase-transfer catalyst, could be used to increase the reactivity of [^{18}F]fluoride in nucleophilic displacement reactions (*2*). The reaction of Kryptofix 222 [^{18}F]fluoride with 1,3,4,6-tetra-*O*-acetyl-2-*O*-trifluoromethanesulfonyl-β-D-manno-pyranose gives 1,3,4,6-tetra-*O*-acetyl-2-[^{18}F]fluoro-β-D-gluco-pyranose with a 95% incorporation of ^{18}F. The overall synthesis, including purification, proceeds in about 60% yield. The synthesis is also technically simple. It involves two steps, displacement of a trifluoromethanesulfonyl group with ^{18}F with [^{18}F]fluoride and removal of the acetyl groups with HCl. This synthesis produces a single isomer (as confirmed by ^{19}F nuclear magnetic resonance of the product from the synthesis with unlabeled fluoride ion) and was an elegant solution to the need to produce ^{18}F-FDG in high yield and in high purity without added carrier.

Over the past three decades, considerable effort has been put into fine tuning the reaction, developing automated radiosynthesis modules, and identifying impurities and contaminants that are carried through to the final product (*4*). This need has become more critical with the increasing use of ^{18}F-FDG in clinical practice, where a pharmaceutical-quality product is required.

In summary, Hamacher's simple and elegant radiosynthesis has made ^{18}F-FDG available for distribution from many central production sites around the world for basic and clinical applications in institutions that have a PET (or PET/CT) scanner but no cyclotron or chemistry infrastructure. This radiosynthesis was transformative. ^{18}F-FDG is now used routinely by many hospitals as an off-the-shelf radiopharmaceutical for clinical research and diagnosis in heart disease, neurologic disorders, and oncology, which is the area of most rapid growth.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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The synthetic procedure starting from [^{18}F]fluoride has several advantages. In contrast to the production of carrier-added ^{18}F by the ^{20}Ne(d,α) ^{18}F reaction in the presence of $^{19}F_2$, the [^{18}F] fluoride can be obtained with very high specific activity (no-carrier-added), e.g., from the nuclear reaction of ^{18}O(p,n) ^{18}F using an oxygen-18 (^{18}O) enriched water target (*13*). This reaction can be carried out with a small 10 MeV proton accelerator.

Three successful nucleophilic syntheses of 2-^{18}FDG are published. One based upon the replacement of the triflate group of methyl 4.6-*O*-benzylidene-3-*O*-methyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranoside by $^{18}F^-$ (*10*) and the other on the reaction of [^{18}F]fluoride with methyl 4.6-*O*-benzylidene-2.3-*O*-sulfuryI-β-D-mannopyranoside (*11*). The substitution of the triflate-group proceeds with a yield of about 30%, but the difficulty in removing the methyl group from the 3-*O*- position reduced the overall yield significantly (~10%). The method developed by Tewson (*11*) leads to an excellent incorporation of $^{18}F^-$ into the cyclic sulfuryl-compound (>90%), but the hydrolysis of the glycoside resulted in a considerable reduction of the radiochemical yield to about 40% or less. A paper has recently been published describing the reaction of anhydrous no-carrier-added KH[^{18}F]F_2 with 1.2-anhydro-3.4:5.6-di-*O*-isopropylidene-l-C-nitro-D-mannitol (*14*). Hydrolysis of the ^{18}F-labeled derivative with trifluoroacetic acid afforded 2-^{18}FDG in a radiochemical yield of 10%.

The goal of this study was to use (a) the tetraacety-lated D-mannose, i.e., 1,3,4,6-tetra-*O*-acetyl-2-trifluor-methanesulfonyl-β-D-mannopyranose (*1*, Fig. 1) as a precursor, and (b) the aminopolyether potassium complex [K/2.2.2]$^+$$^{18}F^-$ as a phase-transfer catalyst. This complex has recently been shown to allow a mild and efficient nucleophilic fluorination at a no-carrier-added level (*15–17*). The resulting increase of nucleophilicity greatly facilitates the fluorination procedure. By using the tetraacetylated precursor which can be selectively prepared (*19*), the removal of the protecting groups can be carried out rapidly under mild conditions and hence higher yields of 2-FDG can be obtained.

MATERIALS AND METHODS

Accelerator Production of [^{18}F]Fluoride

Fluoride-18 was produced* by the ^{20}Ne(d,α)^{18}F reaction using a Ne (15% H_2) target (*18*) to produce no carrier-added ^{18}F-HF, which was removed from the target wall after bombardment by rinsing with triply distilled water. The conversion of no-carrier-added ^{18}F activity to a reproducible and reactive fluoride labeling system using the bicyclic aminopolyether Kryptofix 222† was carried out similar to the method reported previously (*15–17*).

Cold Syntheses

The synthesis and characterization of the precursor 1.3.4.6-tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranose have been published elsewhere (*19*).

For the purpose of confirming the structure of the synthetic product by ^{19}F nuclear magnetic resonance (NMR) spectroscopy, it was necessary to carry out an inactive synthesis to obtain macroscopic amounts of unlabeled 2-fluoro-2-deoxy-D-glucose. The reaction scheme is shown in Fig. 1. The experimental details for the synthesis are as follows: 1.3.4.6-tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranose (0.48 g; 1 mmol) and 0.38 g (1 mmol) of the cryptand Kryptofix 222 were dissolved in 10 ml of dry acetonitrile and heated under reflux for 15 min in

Received May 29, 1985; revision accepted Sep. 18, 1985.
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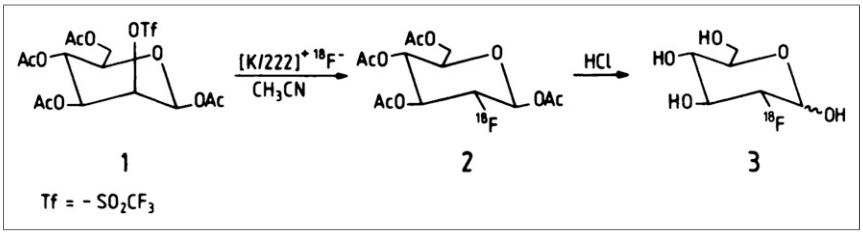

FIGURE 1. Reaction scheme—syntheses of 2-fluoro-2-deoxy-D-glucose.

the presence of 41 mg (0.7 mmol) KF and 25 mg (0.15 mmol) K_2CO_3. The residue was filtered off and the solution concentrated on a rotary evaporator to dryness (bath-temperature <50°C). To remove the phase-transfer catalyst and inorganic components the viscous residue was extracted three times with 5 ml of water and then heated under reflux in the presence of 10 ml of 1*M* hydrochloric acid for 20 min. The acid solution was deionized using ion retardation resin AG11A8 (50-100 mesh)‡, concentrated to dryness and dissolved in D_2O to measure the ^{19}F-NMR spectrum.

Sugar Analysis

The crude reaction mixture of the 2-FDG synthesis was analyzed by anion exchange chromatography (AEC) of the sugar borate complexes. The AEC was performed with an automated sugar analyzer Biotronik ZA 5100§ as described previously (*20*).

Thin layer chromatography (TLC) was performed on silica gel 60† with the solvent system acetonitrile/ water (95:5). The spray reagent orcinol-sulfuric acid was used for detection. The radiochemical purity was ascertained by TLC on monosodium phosphate impregnated silica plates (*12*). This modified TLC method allows the separation of FDG and FDM by developing the plates several times with CH_3CN/ H_2O, (95:5) as eluent. Radio high performance liquid chromatography (HPLC) on Lichrosorb-NH_2 (*10*) (column 250 × 4¶, eluent CH_3CN/ H_2O, 95:5, flow: 1 ml/min) of the no-carrier-added product was compared with authentic samples of 2-FDG/2-FDM.

Reactive [^{18}F]Fluoride Labeling System

In a cylindrical reaction vessel of pyrolytic carbon (Sigradur-G, 18 × 70 mm)** the aqueous solution of no-carrier-added ^{18}F (0.5–1 mCi for the test runs and 20–50 mCi for a production run) was added to a solution of 4.6 mg (0.03 mmol) potassium carbonate and 26 mg (0.06 mmol) Kryptofix 222 in acetonitril-H_2O (86:14) (v/v). At an oil bath temperature of about 105°C the solution was purged with helium (~50 ml/min) and concentrated to dryness. After the solvent was removed (~3 min) the drying process was extended for about 3 min to remove traces of remaining water.

Synthesis of 2-^{18}FDG

A solution of 20 mg (0.04 mmol) 1.3.4.6-tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranose in 1 ml anhydrous acetonitrile was added to the dry residue of [^{18}F] fluoride containing aminopolyether (APE)-complexed potassium carbonate. This mixture was heated under reflux for about 5 min. The solution was concentrated to ~0.4 ml, transferred into a syringe with about 5 ml distilled water, and passed through a C18 SEP-PAK cartridge†† which had been previously washed with 2 ml of THF and 5 ml of water. Residual aminopolyether was desorbed completely by washing the C18 SEP-PAK cartridge with 5 ml of hydrochloric acid (0.1 mol/1). The acetylated carbohydrates were subsequently eluted from the cartridge with 2 ml THF and the solution evaporated to dryness in the Sigradur reaction vessel. Two milliliters of 1*M* hydrochloric acid was added and heated under reflux for 15 min (bath temperature: 130° C). The hydrolysate was decolorized by passing through the same C18 SEP-PAK cartridge as used before. The carbon vessel was rinsed with 1 ml of water and used to elute residual ^{18}FDG from the cartridge. For deionizing the hydrolysate, the acid solution was transferred to a column packed with AG11A8 retardation resin and neutral aluminium oxide 90† (*4*). The resulting neutral eluent was adjusted to an isotonic solution and finally sterilized by passage through a Millipore filter (0.22 μm).

RESULTS AND DISCUSSION

Fluorination of 1.3.4.6-tetra-*O*-acetyl-2-*O*-trifluor-methanesulfonyl-β-D-mannopyranose using APE-complexed potassium fluoride on a macroscopic scale yielded peracetylated 2-fluoro-2-deoxy-D-glucose (*2*, Fig. 1), in ~ 50%. Based on the ^{19}F-NMR data of the crude synthetic product after acid hydrolysis, it is obvious that the nucleophilic substitution gave pure 2-^{19}FDG without any formation of the epimer 2-fluoro-2-deoxy-D-mannose.

The chemical shifts observed were in agreement with data available from the literature for 2-FDG (*4,21*). The δ-values found for 2-FDG were 32.44 ppm (α-anomer) and 32.26 ppm (β-anomer) with a ^{1}H-^{19}F coupling constant of $J_{H\text{-}2,F}$ = 50 Hz and $J_{H\text{-}3,F}$ = 15 Hz, respectively. TLC of the hydrolized crude reaction product showed two major products, with Rf 0.37 identical to 2-FDG and a spot with Rf 0.05 which was due to aldohexoses. Ion exchange chromatography of the sugar borate complexes demonstrated that besides 2–FDG only glucose could be detected in the acid hydrolysate of the crude reaction mixture.

The displacement of the triflate group using the aminopolyether-complexed potassium salt of no-carrier-added [^{18}F] fluoride in the presence of potassium carbonate occurred within less than 5 min (80° C). Although some decomposition was observed during refluxing of acetonitrile, the no-carrier-added [^{18}F]fluoride was incorporated with formation of acetylated 2-^{18}FDG to about 95%. Labeling results of no-carrier-added substitution reaction are reproducible since the amount of [^{18}F] fluoride remaining on the wall of the glassy carbon reaction vessel is <3%. The acetylated 2-^{18}FDG and the excess of triflate were separated from the water-soluble components using a Cl8 SEP-PAK cartridge that adsorbed the lipophilic substances while the hydrophilic aminopolyether (Kryptofix 222) and inorganic salts were eluted completely by water-acetonitrile (90:10) and subsequently washed with 0.1*M* hydrochloric acid. After desorption of the labeled acetylated carbohydrate from the cartridge, the final step was to remove the acetyl groups to give 2-^{18}FDG.

In contrast to the etherified and glycosylated sugar-derivatives (*10,11*) the acetyl groups could be removed easily using acid hydrolysis conditions as described for the corresponding glucal derivative (*9*).

The light-yellow acid hydrolysate containing the unprotected 2-^{18}FDG could be decolorized by filtration through the same Cl8-cartridge used before. The 2-^{18}FDG solution was neutralized by an ion retardation resin and traces of fluoride were adsorbed on aluminium oxide. After this purification step the uncorrected yield of 2-[^{18}F]fluoro-2-deoxy-D-glucose was 44±4% (n = 7) and the total time for the preparation was 45 to 50 min. Within experimental error no change in radiochemical yield was observed for runs

ranging from 1 to 50 mCi of no-carrier-added [^{18}F]fluoride. TLC (MeCN:H_2O/95:5) of the FDG solution has shown that ~ 99% of the [^{18}F] fluorine was present as 2-^{18}FDG (Rf 0.37) whereas only 0.5 to 1% of the $^{18}F^-$ activity was located at the starting point. The TLC on monosodium phosphate impregnated silica plates as described by van Rijn et al. (*12*) makes it feasible to separate the epimeric sugars FDG and FDM. Using this modified TLC method, only one radioactive component with a Rf-value equivalent to that of FDG appeared to be present.

Additionally, the isocratic HPLC (Lichrosorb-NH_2 column) gave the same retention time for the radiochemical product and the authentic 2-FDG sample (HPLC retention time 3.9 min). As in the case of the TLC, radiochemical impurities were not detected.

The nucleophilic ^{18}F fluorination was also performed satisfactorily in anhydrous THF but the reaction time of 25 to 30 min was significantly longer than in the dipolar solvent acetonitrile (5 min).

CONCLUSION

The advantage of the synthetic method presented here is the high yield (max. 55% uncorrected) of no-carrier-added 2-^{18}FDG based on the phase-transfer mediated substitution of triflate by [^{18}F]fluoride. The stereochemical specificity of the nucleophilic displacement combined with a rapid hydrolysis of the acetylated sugar derivative makes it possible to synthesize epimerically pure 2-^{18}FDG with high specific activity. The synthesis of 2-^{18}FDG was carried out successfully with larger quantities of [^{18}F]fluoride suitable for clinical use. In addition, the precursor 1.3.4.6 tetra-*O*-acetyl-2-*O*-trifluormethanesulfonyl-β-D-mannopyranose can be easily prepared in a two step reaction starting with D-mannose.

FOOTNOTES

[*]Jülich (Compact cyclotron CV-28), Jülich, FRG.
[†]E. Merck AG, Darmstadt, FRG.
[‡]BIO-RAD, Richmond, CA.
[§]Biotronik, Munich, FRG.
[¶]Merck, Darmstadt, FRG.
[**]SIGRI, Meitingen, FRG.
[††]Waters Chromatography Div., Millipor, MA.

ACKNOWLEDGMENTS

The authors thank Mr. G. Blessing for carrying out the ^{18}F production and Mr. P. Laufer for performing the NMR analyses.

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