8 (1.665 g, 95%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.23 (3 H, t, J = 7.45 Hz), 2.50 (2 H, br s), 3.35 (2 H, d, J = 5.43 Hz), 3.70 (2 H, m), 3.82 (3 H, s), 4.13 (3 H, m), 6.92 (2 H, m), 7.28 (2 H, m); IR (NaCl, neat) 3310, 2910, 1735, 1595, 1485, 1455, 1230, 1180, 1020, 740 cm^{-1}; mass spectrum, CI (NH_3) m/z 254 (M^+, 1.9), 236 (1.8), 208 (18.9), 168 (2.5), 150 (6.7), 130 (61.1), 104 (11.3), 72 (7.2), 55 (100).

Cyclic Urethane 9. To a stirred solution of **8** (1.665 g, 6.59 mmol, 1.0 equiv) in dry THF (60 mL) was added *N*,*N*′-carbonyldiimidazole (1.60 g, 9.87 mmol, 1.5 equiv). The resulting solution was stirred at room temperature for 2 h and evaporated to a white residue. The residue was taken up in CH_2Cl_2 (100 mL), washed with 1 M HCl (3 × 25 mL), H_2O (2 × 25 mL), and brine (1 × 25 mL), dried over $MgSO_4$, filtered, and evaporated, yielding **9** as a colorless oil (1.41 g, 77%): ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.25 (3 H, t, J = 7.03 Hz), 3.43 (1 H, d, J = 17.96 Hz), 3.82 (3 H, s), 4.16 (3 H, m), 4.34 (1 H, d, J = 17.98 Hz), 4.72 (1 H, t, J = 8.67 Hz), 5.35 (1 H, m), 6.97 (2 H, m), 7.27 (2 H, m); IR (NaCl, neat) 2960, 2920, 2820, 1750, 1600, 1580, 1485, 1460, 1415, 1240, 1195, 1080, 1115, 745 cm^{-1}. Mass spectrum, CI (NH_3) m/z 280 (M^+, 54.9%), 250 (3.1), 235 (1.2), 220 (1.4), 162 (1.8), 148 (1.7), 133 (2.0), 104 (1.7), 35 (100).

Carboxylic Acid 10. To a stirred solution of **9** (1.41 g, 5.059 mmol, 1.0 equiv) in 16 mL of absolute ethanol at −10 °C was added 6.7 mL of 1 M LiOH (6.7 mmol, 1.32 equiv). The reaction was allowed to stir for 1.5 h at −10 °C and was then neutralized with 6 M HCl (1.11 mL, 6.7 mmol, 1.32 equiv). The ethanol was evaporated, and the resulting residue was partitioned between 1 M HCl and CH_2Cl_2. The organic layer was separated, washed with H_2O (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered, and evaporated to a white solid. Recrystallization from EtOAc/hexanes afforded 957 mg of pure **10** (75%): mp 165–166 °C; ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.48 (1 H, d, J = 18.25 Hz), 3.83 (3 H, s), 4.19 (1 H, t, J = 8.02 Hz), 4.39 (1 H, d, J = 18.438 Hz), 4.73 (1 H, t, J = 9.174 Hz), 5.36 (1 H, m), 6.95 (2 H, m), 7.36 (2 H, m), 8.52 (1 H, br s); IR (NaCl, neat) 2900, 2810, 2700, 2585, 2500, 1750, 1675, 1595, 1580, 1450, 1240, 1200, 1190, 1110, 940, 850, 750, 735, 700, 630 cm^{-1}; mass spectrum, CI (NH_3) m/z 251 (M^+, 13.8%), 236 (3.5), 208 (7.9), 194 (6.6), 164 (2.5), 150 (5.5), 135 (4.1), 102 (3.7), 76 (3.2), 44 (8.1), 35 (100). Anal. ($C_{12}H_{13}NO_5$) C, H, N.

Acid Chloride 11. To a suspension of **10** (408 mg, 1.626 mmol, 1.0 equiv) in dry benzene (8 mL) was added $SOCl_2$ (0.36 mL, 4.91 mmol, 3.02 equiv). The suspension was then heated to mild reflux for 3 h, and the benzene and $SOCl_2$ were evaporated under reduced pressure. The resulting light amber residue (438 mg, 100%) was used directly for the next step without purification: ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.78 ($^1/_2$ H, s), 3.84 (3.5 H, s), 4.25 (1 H, dd, J = 8.63 Hz), 4.73 (2 H, m), 5.32 (1 H, dd, J = 9.02 Hz), 6.97 (2 H, m), 7.27 (2 H, m); IR (NaCl, neat) 3060, 3020, 2940, 2830, 1800, 1760, 1600, 1590, 1490, 1460, 1420, 1250, 1180, 1110, 1090, 1020, 950, 920, 850, 750, 670 cm^{-1}.

Isoquinolone 12. To a stirred solution of **11** (438 mg, 1.626 mmol, 1.0 equiv) in 16 mL of dry 1,1,2,2-tetrachloroethane was added $AlCl_3$ (867 mg, 6.5 mmol, 4.0 equiv). The reaction was stirred at room temperature for 24 h, when it was poured into 40 mL of ice water and acidified to pH <2 with concentrated HCl. The resulting slurry was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic extracts were washed with 1 M NaOH (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered, and evaporated to an oil, which was separated by column chromatography (silica gel, 3:2 hexanes/EtOAc), yielding **12**: 246 mg, 65%; mp 157–159 °C dec (recrystallized from EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.83 ($^1/_2$ H, s), 3.91 (3.5 H, s), 4.25 (1 H, t, J = 8.54 Hz), 4.67 (1 H, d, J = 18.15 Hz), 5.03 (1 H, t, J = 8.94 Hz), 5.23 (1 H, t, J = 8.61 Hz), 7.16 (1 H, dd, J = 8.28 Hz), 7.46 (1 H, t, J = 8.41 Hz), 7.73 (1 H, dd, J = 8.14 Hz); IR (NaCl, neat) 3080, 3020, 2940, 2870, 1765, 1695, 1595, 1580, 1430, 1280, 1250, 1120, 1030, 785, 740, 670 cm^{-1}; mass spectrum, CI (NH_3) m/z 233 (M^+, 16.9%), 219 (7.9), 189 (2.1), 174 (7.4), 159 (2.8), 132 (1.3), 35 (100). Anal. ($C_{12}H_{11}NO_4$) C, H, N.

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Lithium-Selective, Lipophilic, Small-Ring Bis(crown ethers)

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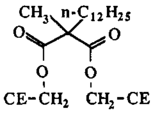
Bis(crown ethers) may exhibit highly selective alkali metal cation complexation by formation of intramolecular complexes in which the cation is sandwiched between the two adjacent crown ether rings.[1] Ion-selective, bis(crown ether) esters derived from dodecylmethylmalonic acid and hydroxymethyl-substituted crown ethers have been found to be selective for the alkali metal cation that is slightly larger than the crown ether cavity. Thus, for bis(crown ether) esters **1** in which CE corresponds to 12-crown-4, 15-crown-5, and 18-crown-6 rings, selectivity for Na^+, K^+, and Cs^+, respectively, has been reported.[2-4] Similarly, the complex stability constants for interactions of Na^+ and K^+ with **1** where CE = 12-crown-4 in MeOH gave a Na^+/K^+ selectivity of 34.[5] Also, in extractions of aqueous Na^+, K^+, Rb^+, and Cs^+ picrate solutions with dichloromethane solutions of the malonate bis(12-crown-4) compound **2**, the distribution ratios for Na^+ picrate were the highest by a considerable margin.[6]



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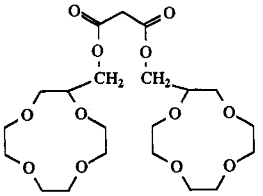

2

By analogy, malonate-type bis(crown ethers) with very small crown ether rings might be expected to exhibit selectivity for complexation of Li^+. We now report the synthesis of new lipophilic bis(crown ethers) **3**–**5**, which have 9-crown-3, 12-crown-4, and 14-crown-4 ring sizes, respectively, and comparison of their efficiencies for extraction of Li^+, Na^+, K^+, and Rb^+ picrates into deuteriochloroform. For **3** and **4**, the crown ether rings are too small to accommodate even Li^+, whereas for **5**, the crown ether ring size is appropriate for Li^+ complexation.[7-10]

Previously unreported (hydroxymethyl)-9-crown-3 (**6**) was prepared in high yield by an Okahara cyclization[11] of

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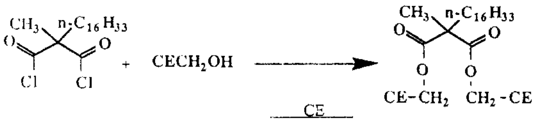
Table I. Extraction Constants (K_{ex}) and Association Constants (K_a) for Cation Complexation by Bis(crown ethers) 3–5

	log K_{ex}[a]				log K_a[b]			
compd	Li^+	Na^+	K^+	Rb^+	Li^+	Na^+	K^+	Rb^+
3	3.58	2.81	1.91	1.87	6.42	5.57	4.50	4.21
4	4.84	3.34	2.73	2.72	7.69	6.14	5.33	5.06
5	3.53	2.79	1.90	1.88	6.38	5.53	4.51	4.22

[a] Deuteriochloroform–water system at room temperature (22–23 °C). [b] In deuteriochloroform.

3,6-dioxa-4-[(benzyloxy)methyl]-1,8-octanediol[12] followed by debenzylation. Hexadecylmethylmalonyl chloride was synthesized by alkylation of diethyl hexadecylmalonate under PTC conditions, followed by basic hydrolysis and reaction of the resulting diacid with oxalyl chloride. Bis(crown ethers) **3–5** were obtained in 62–68% yields by reactions of hexadecylmethylmalonyl chloride with hydroxymethyl-substituted crown ethers **6–8**, respectively (eq 1).



(1)

	CE	
6	9-Crown-3	3
7	12-Crown-4	4
8	14-Crown-4	5

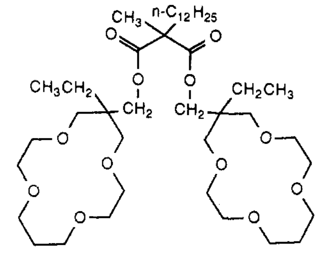
The Li^+, Na^+, K^+, and Rb^+ complexing abilities of bis(crown ethers) **3–5** were assessed by solvent extraction of aqueous metal picrate solutions with deuteriochloroform solutions of the ionophore.[13,14] Extraction constants, K_{ex}, and association constants in deuteriochloroform, K_a, were evaluated in the customary manner.[13,14] Data are presented in Table I.

The picrate extraction data for the bis(9-crown-3) compound **3** reveals a cation extraction selectivity order of $Li^+ > Na^+ > K^+ > Rb^+$ with a $K_a(Li^+)/K_a(Na^+)$ selectivity ratio of 7. Bis(crown ether) esters **4** and **5**, which have somewhat larger crown ether rings, exhibit the same cation extraction selectivity order and $K_a(Li^+)/K_a(Na^+)$ selectivity ratios of 37 and 7, respectively.

The high Li^+ selectivity in alkali metal picrate extractions by bis(12-crown-4) compound **4** contrasts sharply with the reported[6] high Na^+ selectivity for alkali metal picrate extractions by the closely related bis(12-crown-4) ester **2**. This difference may be attributed simply to a failure to include Li^+ picrate in the earlier study.[6] Indeed, when the reported distribution ratios for extractions of Na^+ and K^+ picrates with **2** are converted into extraction constants in dichloromethane, log K_{ex} values of 3.50 and 2.47, respectively, are calculated. These numbers compare favorably with the log K_{ex} values for complexation of Na^+ and K^+ picrates by **4** in deuteriochloroform that were determined in the present study (Table I).

In a PVC membrane electrode that utilized lipophilic bis(12-crown-4) ester **1** (CE = 12-crown-4) as the ionophore, excellent response to aqueous NaCl solutions with only very slight interference from LiCl in mixed solutions was noted.[2] Comparison of this result with that described above for picrate extractions by bis(12-crown-4) compound **4** strongly suggests that the nature of the aqueous-phase anion plays an important role in determining the relative efficiencies with which bis(crown ether) esters can extract alkali metal cations into lipophilic media.

Very recently, a paper appeared in which Li^+ selectivity over Na^+ and K^+ was noted for the lipophilic bis(14-crown-4) ester **9** in a PVC membrane electrode.[15] Comparison with results for closely related compounds that have a single modified 14-crown-4 ring strongly suggests that the two crown ether rings in **9** interact independently in complexing Li^+. Although similar arguments might be advanced to explain the Li^+ selectivity for bis(14-crown-4) ester **5** in the present study, the much higher Li^+ selectivity of the corresponding bis(12-crown-4) compound **4** clearly must result from formation of a sandwiched complex since the crown ether rings are too small to accommodate even Li^+.



9

Experimental Section

IR spectra were obtained on neat samples and are reported in reciprocal centimeters. ^1H NMR spectra were recorded with a Varian EM360 or EM360A spectrometer in deuteriochloroform and are reported in parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained with a Hewlett Packard 5595B GC/MS. Visible spectra were recorded with a Perkin Elmer Lambda 5 UV-vis spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., of Knoxville, TN. Unless specified otherwise reagent grade reactants and solvents were obtained from chemical suppliers and used as received. (Hydroxymethyl)-12-crown-4 (**7**),[9] (hydroxymethyl)-14-crown-4 (**8**),[9] and 3,6-dioxa-4-[(benzyloxy)methyl]-1,8-octanediol[12] were prepared by literature methods.

(Hydroxymethyl)-9-crown-3 (6). A solution of 3,6-dioxa-4-[(benzyloxy)methyl]-1,8-octanediol (10.0 g, 40 mmol) and *p*-toluenesulfonyl chloride (8.3 g, 40 mmol) in 300 mL of dry dioxane was added during 10 h to a stirred mixture of powdered LiOH (6.4 g, 160 mmol) in 200 mL of dry dioxane at 60 °C under nitrogen. The reaction mixture was stirred at 60 °C for an additional 10 h and filtered. Evaporation of the filtrate in vacuo gave a crude product that was chromatographed on alumina with CH_2Cl_2 as eluent to give 7.2 g (72%) of [(benzyloxy)methyl]-9-crown-3 as an extremely hydroscopic colorless oil: IR 1116 (C–O); ^1H NMR δ 3.4–3.9 (m, 13 H), 4.54 (s, 2 H), 7.33 (s, 5 H). Anal. Calcd for $C_{14}H_{20}O_4 \cdot 0.3H_2O$: C, 65.10; H, 8.04. Found: C, 64.98; H, 7.93.

The [(benzyloxy)methyl]-9-crown-3 (6.9 g, 27.4 mmol), 0.02 g of *p*-toluenesulfonic acid, and 0.70 g of 10% Pd/C in EtOH (100 mL) were shaken under H_2 (40 psi) for 24 h. The reaction mixture was filtered and the solvent was evaporated in vacuo to produce a colorless oil that was purified by chromatography on alumina with EtOAc as eluent to give 4.5 g (85%) of (hydroxymethyl)-9-crown-3 (**6**) as an extremely hygroscopic colorless oil: IR 3418 (O–H), 1103 (C–O); ^1H NMR δ 3.70 (s); MS, *m/e* 163.1 ($M \cdot H^+$).

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Anal. Calcd for $C_7H_{14}O_4{\cdot}0.5H_2O$: C, 48.56; H, 8.74. Found: C, 48.20; H, 8.60.

Hexadecylmethylmalonyl Chloride. A solution of diethyl hexadecylmalonate (5.0 g, 16.6 mmol) and MeI (14.2 g, 97 mmol) in 25 mL of CH_2Cl_2 was stirred with tetra-*n*-butylammonium chloride (11.3 g, 50 mmol) and NaOH (4.0 g, 100 mmol) in 75 mL of H_2O for 1 h at room temperature. The CH_2Cl_2 layer was separated and evaporated in vacuo. After addition of Et_2O (100 mL), filtration, drying ($MgSO_4$), and evaporation in vacuo, the residue was chromatographed on silica gel with CH_2Cl_2 as eluent to provide 4.5 g (86%) of diethyl hexadecylmethylmalonate as a colorless oil: IR 1747 (C=O); ^{1}H NMR δ 0.75–2.15 (m, 42 H), 4.0–4.5 (q, 4 H); MS, *m/e* 398.6 (M^+). Anal. Calcd for $C_{24}H_{46}O_4$: C, 72.31; H, 11.63. Found: C, 72.27; H, 11.62.

Diethyl hexadecylmethylmalonate (4.0 g, 10 mmol) was added to 50% aqueous NaOH (50 mL) and the reaction mixture was refluxed for 12 h, acidified to pH 1 with 6 N HCl, and extracted with EtOAc (50 mL). The EtOAc layer was washed with H_2O (50 mL), dried ($MgSO_4$), and evaporated in vacuo to give a quantitative yield of hexadecylmethylmalonic acid as a white solid with mp 60–61 °C: IR 3600–2400 (O–H), 1745 (C–O); ^{1}H NMR δ 0.75–2.15 (m). Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.15; H, 10.95.

Hexadecylmethylmalonic acid (3.0 g, 8.8 mmol) was stirred with 5 mL of oxalyl chloride in 20 mL of dry benzene at room temperature for 12 h under nitrogen. The solvent was evaporated in vacuo and 50 mL of 30–60 °C petroleum ether was added to the residue. Filtration and evaporation of the solvent gave a quantitative yield of hexadecylmethylmalonyl chloride as a colorless oil: IR 1763 (C=O); ^{1}H NMR δ 0.75–2.15 (m).

General Procedure for Preparation of Bis(crown ether) Esters 3–5. A solution of the appropriate hydroxymethyl crown ether (40 mmol) in 25 mL of dry C_6H_6 was added to a solution of hexadecylmethylmalonyl chloride (20 mmol) in dry C_6H_6 (50 mL) and pyridine (30 mL). The solution was refluxed for 24 h under nitrogen and evaporated in vacuo to give an oil that was dissolved in EtOAc (100 mL). The EtOAc solution was washed with 5% aqueous AcOH, dried ($MgSO_4$), and evaporated in vacuo to give a crude product, which was chromatographed on silica gel with CH_2Cl_2 and CH_2Cl_2–MeOH (20:1) as eluents to afford the product as a yellow oil.

Bis(crown ether) 3 was obtained in 63% yield: IR 1745 (C=O), 1103 (C—O); ^{1}H NMR δ 0.8–2.0 (m, 36 H), 3.4–4.45 (m, 26 H). Anal. Calcd for $C_{34}H_{62}O_{10}$: C, 64.73; H, 9.91. Found: C, 64.52; H, 10.22.

Bis(crown ether) 4 was produced in 62% yield: IR 1732 (C=O), 1132 (C—O); ^{1}H NMR δ 0.8–1.9 (m, 36 H), 3.4–4.35 (m, 34 H). Anal. Calcd for $C_{38}H_{70}O_{12}$: C, 63.48; H, 9.81. Found: C, 63.36; H, 9.82.

Bis(crown ether) 5 was formed in 68% yield: IR 1745 (C=O), 1130 (C—O); ^{1}H NMR δ 0.6–1.6 (m, 36 H), 1.7–2.4 (m, 6 H), 3.45–4.15 (m, 36 H). Anal. Calcd for $C_{42}H_{78}O_{12}{\cdot}0.5H_2O$: C, 64.34; H, 10.14. Found: C, 64.43; H, 10.16.

Picrate Extractions into Deuteriochloroform. Bis(crown ether) solutions (15 mM) were prepared in ethanol-free deuteriochloroform. With use of the reported procedure,[13,14] extractions were conducted by adding 0.50 mL of the 15 mM bis(crown ether) solution in deuteriochloroform to 0.50 mL of a 15 mM alkali metal picrate solution in a centrifuge tube, and the mixture was vigorously agitated with a vortex mixer for 1 min. Five identical samples were run concurrently. The mixtures were centrifuged for 10 min and allowed to stand overnight to assure complete layer separation. Precisely measured aliquots were removed from each layer with microsyringes and diluted in THF. Visible spectra of these solutions were measured in the region of 340–550 nm. In all cases, the picrate absorption maxima were in the region of 343–351 nm, which is characteristic of a tight ion pair.[16] From the alkali metal picrate concentrations in each phase, the K_{ex} (extraction constant) value was calculated[13,14] and converted into the K_a (association constant in deuteriochloroform) value by the reported method. In the calculations, exclusive formation of complexes of one alkali metal cation with one bis(crown ether) was assumed.

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Registry No. 3, 108269-91-6; 4, 87377-17-1; 5, 108269-92-7; 6, 108269-93-8; 7, 75507-26-5; 8, 92818-21-8; $(ClCO)_2C(CH_3)(CH_2)_{15}CH_3$, 108269-94-9.

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The Reaction of Various Methoxy-Substituted Haloarenes with Amines and Nitriles under Aryne-Forming Conditions

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We[1-4] have shown recently that good yields of a single product are obtained via the aryne of disubstituted haloaromatic compounds if the aryne intermediate is either symmetric or is unsymmetric but possesses strongly electron-attracting groups such as methoxy. The aryne reaction of polymethoxyhaloarenes is particularly interesting since methoxy substituents are commonly found in many biologically active compounds. Thus, 2-bromo-1,4-dimethoxybenzene, in the presence of sodamide and various primary and secondary amines, yields *N*-alkyl- and *N,N*-dialkyl-2,5-dimethoxyanilines, respectively, via the symmetrical aryne intermediate, 3,6-dimethoxybenzyne.[1] This bromoarene also reacts with nitrile anions in liquid ammonia under aryne-forming conditions, affording mainly 2-(cyanoalkyl)-1,4-dimethoxybenzenes and small amounts of 2,5-dimethoxyaniline.[1]. The isomeric intermediate, 3,4-dimethoxybenzyne, generated from 4-bromo-1,2-dimethoxybenzene is unsymmetric; however, it is aminated in the presence of primary and secondary amines regioselectively at 1-position yielding cine substitution products, *N*-alkyl- and *N,N*-dialkyl-3,4-dimethoxyanilines, respectively.[2] In presence of nitrile anions and liquid ammonia, that unsymmetric aryne reacts regioselectively and solely with the less reactive but more abundant ammonia solvent affording 3,4-dimethoxyaniline.[2] The meta-directing effect of the methoxy group is well-known.[5] It has been also shown to increase the reactvity of benzyne by inductively polarizing the "triple bond".[6] The greater selectivity of the symmetric 3,6-dimethoxybenzyne as compared to the unsymmetric 3,4-dimethoxybenzyne is due, partly, to the cancelling of the inductive effect of the two methoxy groups polarizing the "triple bond".

In order to obtain further information on the influence of two or more substituents on the regioselectivity and reactivity of benzyne, the reactions of 4-bromo-1,3-dimethoxybenzene (1), 4-bromo-1,2,3-trimethoxybenzene (2), and 2-bromo-4-methylanisole (3), with various amines and niiriles under aryne-forming conditions were studied.

Results and Discussion

Reaction of 1, 2, and 3 with Primary and Secondary Amines. The results of the reaction of 1, 2, and 3 with various amines are listed in Table I. The data show that each haloarene undergoes predominantly cine substitution,

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