Synthesis of Carbon-Linked Bis(chromium carbene) Complexes, Bis(azapenams), and Bis(dioxotetraazacyclotetradecadienes)

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Carbon-linked bis(chromium carbene) complexes were synthesized by the bis-alkylation of 1,*n*-alkyl bis(triflates). Photolysis with N-protected imidazolines followed by deprotection and acid-catalyzed dimerization produced bis(dioxotetraazacyclododecadienes) linked by five- or six-carbon aliphatic chains.

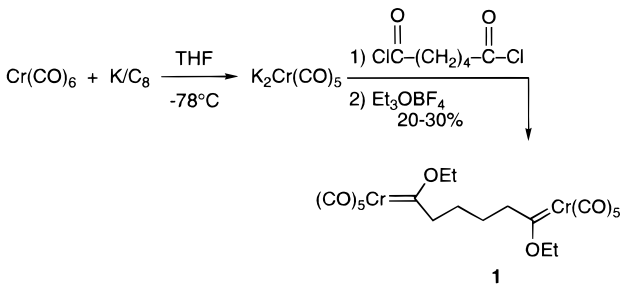
Introduction

Recent studies in these laboratories have centered on the use of photochemical reactions of chromium alkoxycarbene complexes[1] with imidazolines to produce azapenams. Acid-catalyzed cleavage of these produced seven-membered cyclic imines, which spontaneously dimerized to produce dioxotetraazacyclotetradecadienes,[2] 14-membered tetraazamacrocycles related to dioxocyclams. Bis(carbene) complexes linked through the alkoxy groups were readily prepared from 1,*n*-diols. These, in turn, were used to synthesize alkoxy-linked bis(tetraazamacrocycles) of potential use as ligands for the development of new catalysts and as hosts in host−guest chemistry.[3]

Although ether linkages are chemically robust, they can be cleaved by strongly acidic conditions, particularly when the ether center is tertiary as it is in these bis(macrocycles). Carbon-linked bis(carbene) complexes of group 6 metals have been synthesized by the conjugate addition of α-lithio carbanions of tungsten[4] and chromium[5] alkoxycarbene complexes with α,*β*-unsaturated carbene complexes (Michael addition), by the reaction of chromium hexacarbonyl with 1,10-dilithio-1,9-decadiene,[6] by the reaction of α-lithio carbanions of tungsten aminocarbene complexes with diiodoalkanes,[7] by the reaction of α-lithio carbanions of chromium alkoxycarbene complexes with tetrachlorocyclopropene,[8] and by the aldol condensation of chromium alkoxycarbene complexes with aromatic dialdehydes.[9] Alkynediyl-bridged bis(carbene) complexes have been synthesized by Stille coupling.[10] The results of studies directed toward the synthesis of aliphatic hydrocarbon-linked bis(carbene) complexes and their use in the synthesis of carbon-linked bis(tetraazamacrocycles) are reported below.

Results and Discussion

Acid chlorides undergo reaction with the highly nucleophilic chromium pentacarbonyl dianion (Cr^{2-}) to produce anionic acyl complexes, which upon treatment with hard alkylating agents generates alkoxy−carbene complexes.[11] Treatment of adipoyl chloride with dipotassium chromium pentacarbonyl followed by treatment with triethyloxonium tetrafluoroborate produced the desired carbon-linked bis(carbene) complex **1** in modest yield (eq 1). Despite attempts to optimize this process,



(1)

the yields remained low and the reaction proved very sensitive to reaction conditions, necessitating a different approach.

Generation of the α-lithio carbanion of the ((methoxy)(methyl)carbene)chromium complex by treatment with *n*-butyllithium, followed by reaction with 1,4-dibromo- or 1,4-diiodobutane, resulted in no reaction, despite the reported success of similar reaction chemistry with the tungsten analogue. In contrast to alkyl halides, alkyl triflates had sufficient reactivity to form carbon-linked bis(carbene) complexes in modest yield (eq 2).

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(2) (a) Betschardt, C.; Hegedus, L. S. *J. Am. Chem, Soc.* **1992**, *114*, 5010. (b) Hegedus, L. S.; Moser, L. S. *J. Org. Chem.* **1994**, *59*, 7779.
(3) Dumas, S.; Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3368.
(4) Macomber, D. W.; Hung, M.-H.; Verma, A. G. *Organometallics* **1988**, *7*, 2072.
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(10) Hartbaum, C.; Mauz, E.; Roth, G.; Weissenbach, K.; Fischer, H. *Organometallics* **1999**, *18*, 2619.
(11) (a) Semmelhack, M. F.; Lee, G. R. *Organometallics* **1987**, *6*, 1839. (b) Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264. (c) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814.

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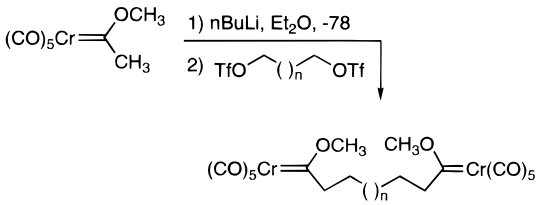
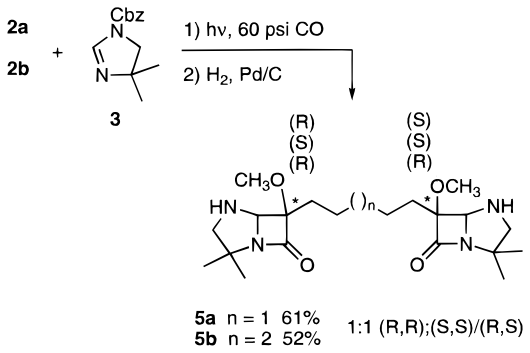


(2)

The reaction with the 1,4-butanediol bis(triflate) always produced varying amounts of cyclopentylcarbene complex, from intramolecular double alkylation of the starting carbene complex. This could be suppressed to a degree by using high-dilution conditions. The use of potassium counterion (from KHMDS) or of 12-crown-4 to coordinate the lithium of the α-lithio carbanion *increased* the amount of this undesired intramolecular double alkylation. This intramolecular double alkylation was not observed with the 1,3-propanediol bis(triflate), since this would produce a strained four-membered ring. Attempts to improve the yield with both substrates by utilizing the more nucleophilic[12] (triphenylphosphine)-tetracarbonylchromium carbene complex had little effect and suffered from the subsequent requirement of separating the phosphine from the carbene complex.

Photolysis of carbene complexes **2a,b** with N-protected imidazolines produced bis(azapenams) after removal of the protecting group. Achiral imidazoline **3**, lacking



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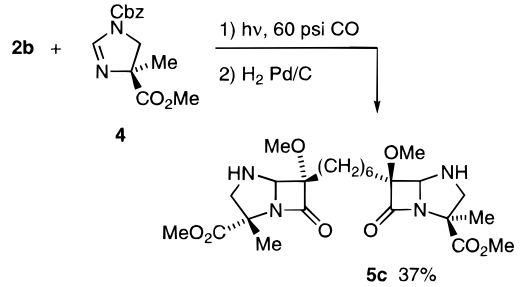
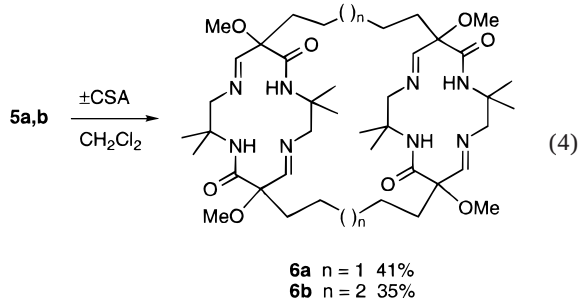


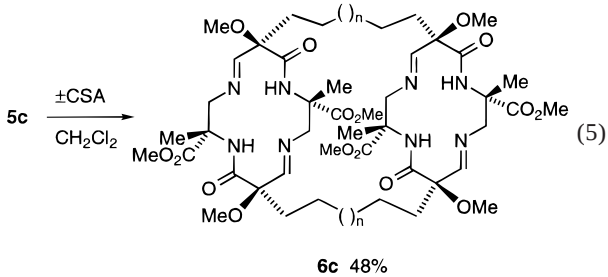
an element of stereocontrol, must produce a mixture of diastereoisomeric bis(azapenams), the racemic *R,R*/*S,S* C_2-symmetric compounds as well as the centrosymmetric *R,S* compound. With 1,5-*diether* linkages these diastereoisomers were different by both ^{1}H and ^{13}C NMR spectroscopy[3] and could be separated. In marked contrast, the ^{1}H NMR spectra of carbon-linked bis(azapenams) **5a**,**b** each appear as if they were of single diastereoisomers (that is, there is only one set of peaks for each kind of proton), while the ^{13}C spectra show doubling of only a few peaks in the δ 20−30 ppm region of the spectra, indicative of the obligate presence of diastereoisomers. As expected,[13] the use of optically active imidazoline **4** produced a single diastereoisomer of bis(azapenam) **5c**.

Treatment of bis(azapenams) **5a,b** with (±)-camphorsulfonic acid in methylene chloride resulted in dimerization to produce bis(dioxotetraazacyclododecadienes) **6a,b** in fair yield (eq 4). Since a diastereoisomeric



(4)

mixture of bis(azapenams) **5a,b** was used, the resulting bis(macrocycles) were expected to also be mixtures of diastereoisomers. In principle, eight different diastereoisomeric bis(macrocycles) could form from all possible combinations of the three diastereoisomeric bis(azapenams). In practice, this dimerization displays an overwhelming preference for the dimerization centers of *like* configuration[3] (*R* → *R*, *S* → *S*, "homo" dimers), limiting the diastereoisomers of **6a,b** to the C_2-symmetric *d*,*l* pair (*R* → *R*; *R* → *R*) and (*S* → *S*; *S* → *S*) and the centrosymmetric homo dimer (*R* → *R*; *S* → *S*). Indeed, the ^{1}H NMR spectrum of **6a** clearly showed the presence of two diastereoisomers (two amide N−H peaks at δ 9.0, 9.8, two OMe peaks at δ 3.21, 3.23) as well as doubling of a number of peaks in the ^{13}C NMR spectrum. In contrast, **6b**, with a longer linker and, as a consequence, a greater distance between the chiral centers, appeared by ^{1}H and ^{13}C NMR spectroscopy to be a single diastereoisomer, while, in fact, it must be a mixture. (Similar observations were made with longer chain diether linked bis(macrocycles).[3]) Dimerization of optically active bis(azapenam) **5c** produced optically active bis(macrocycle) **6c** in modest yield, as a single diastereoisomer (eq 5).



(5)

In marked contrast to the alkoxy-linked bis(dioxotetraazacyclododecadienes), compounds **6a**−**c** could not be cleanly reduced to the saturated analogues. Catalytic hydrogenation (H_2 Pd/C) resulted in no reaction, while the normal[3] sodium cyanoborohydride reducing conditions decomposed the compounds. This, coupled with the

(12) Xu, Y.; Wulff, W. D. *J. Org. Chem.* **1987**, *52*, 3263.

(13) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *63*, 3586.

inseparability of diastereoisomers, will limit the utility of this class of macrocyclic ligand.

Experimental Section

General Information. All NMR spectra (300 MHz for ^{1}H NMR and 75 MHz, for ^{13}C NMR) were recorded in $CDCl_3$, and chemical shifts were given in δ relative to TMS (δ 0.00 for ^{1}H) and $CDCl_3$ (δ 77.0 for ^{13}C) unless otherwise stated. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR.

The following compounds were prepared according to literature methods: pentacarbonyl((methoxy)(methyl)carbene)-chromium,[14] 1,4-bis((trifluoromethyl)sulfonyl)butane,[15] 1-((benzyloxy)carbonyl)-4,4-dimethyl-Δ^2-imidazoline, and (*S*)-1-((benzyloxy)carbonyl)-4-methyl-4-carbomethoxy-Δ^2-imidazoline.

1,3-Bis((trifluoromethyl)sulfonyl)propane. Into a dry addition funnel attached to a 100 mL round-bottom flask was placed 1.0 g (13.8 mmol) of 1,3-propanediol, 2.3 g (29.1 mmol) of pyridine, and 13 mL of CH_2Cl_2. Into the flask was placed 8.2 g (29.1 mmol) of trifluoromethanesulfonic anhydride and 25 mL of CH_2Cl_2. The flask was cooled to 0 °C under Ar. The diol solution was added dropwise to the anhydride. The solution was warmed to room temperature for 1 h. The organic solution was washed with water (2 × 20 mL) and dried over Na_2SO_4. The solvent was removed to yield 3.16 g (9.3 mmol 71%) of a clear oil. This highly reactive material was used without further purification. ^{1}H NMR: δ 4.6 (t, J = 5.5 Hz, 4H), 2.4 (p, J = 5.5 Hz, 2H).

Bis(carbene) Complex 2a. Into a dry 1 L two-necked round-bottom flask with an attached addition funnel was placed 1.6 g (6.47 mmol) of (methoxy)(methyl)carbene complex and 130 mL of dry ether. To the addition funnel was added 0.996 g (2.9 mmol) of 1,3-bis((trifluoromethyl)sulfonyl)propane and 250 mL of dry ether. The flask was cooled to −78 °C under argon, and 4.2 mL (6.72 mmol) of *n*-BuLi was added via syringe. The solution was stirred for 20 min. A solution of trifluoromethanesulfonate was slowly added over 2 h. The reaction mixture was then warmed to 0 °C for 2 h. It was then washed with 300 mL of 5% $NaHCO_3$ (aqueous), 300 mL of water, and 300 mL of brine. The organic layer was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure in the dark and purified quickly using a silica gel column with hexanes as eluent to 2% ethyl acetate/hexanes to yield 483 mg (0.894 mmol, 30%) of a yellow oil. ^{1}H NMR: δ 4.7 (br s, 6H), 3.2 (t, 4H, J = 7.5 Hz), 1.5−1.3 (m, 6H). ^{13}C NMR: δ 363.0, 222.9, 216.0, 67.0, 62.0, 28.6, 25.5. IR (film): ν 2953, 1946 cm^{-1}. HRMS (FAB): m/z calculated for $C_{19}H_{16}Cr_2O_{12}$ (M^+) 539.9452, found 539.9458.

Bis(carbene) Complex 2b. Bis(carbene) complex **2b** was synthesized in a method similar to that for **2a**, starting with 1.55 g (6.2 mmol) of (methoxy)(methyl)carbene complex in 124 mL of dry ether, 1.00 g (2.8 mmol) of 1,4-bis((trifluoromethyl)-sulfonyl)butane in 250 mL of dry ether, and 3.9 mL (6.24 mmol) of *n*-BuLi to yield 0.989 g (1.8 mmol, 63%) of the product as a yellow solid. ^{1}H NMR: δ 4.8 (s, 6H), 3.3 (t, 4H, J = 7.5 Hz), 1.25−1.6 (m, 8H). ^{13}C NMR: δ 363, 223, 216, 67.6, 62.8, 28.8, 26.0. IR (film): ν 2062, 1932 cm^{-1}. Anal. Calcd for $C_{20}H_{18}Cr_2O_{12}$: C, 43.33; H, 3.27. Found: C, 43.35; H, 2.91.

Bis(azapenam) 5a. Into a dry pressure tube was placed 0.300 g (0.56 mmol) of **2a**, 0.245 g (1.06 mmol) of imidazoline **3**, and 22 mL of CH_2Cl_2. This mixture was freeze−pump−thaw-degassed three times. It was then flushed with 80 psi of CO three times and irradiated (4 × 500 W halogen lamps) at 50 °C until the yellow color had faded (about 6 h). The solvent was removed, and the residue was dissolved into methanol and placed into the freezer. The $Cr(CO)_6$ was removed by filtration, and the solvent was removed under reduced pressure. This residue was dissolved in 1:1 hexane−ethyl acetate and exposed to air and sunlight (2 days or until clear). The solution was filtered, and the solvent was removed. Purification was accomplished on silica gel using 1:1 hexane−ethyl acetate to yield 0.236 g (0.35 mmol, 62%) of product.

The bis(azapenam) (0.339 g, 0.50 mmol) was dissolved in 25 mL of dry MeOH along with 200 mg of Pd/C (5%) and 30 drops of triethylamine. The pressure tube was charged with 80 psi H_2 and stirred for 2 h. The palladium was removed by filtration, and the solvent was removed to give 0.202 g (0.49 mmol, 99%) of a white solid. ^{1}H NMR: δ 6.5 (s, 2H), 3.41, (s, 6H), 3.1 (d, J = 11.4 Hz, 2H), 2.62, (d, J = 11.4 Hz, 2H), 2.2, (br s, 2H), 1.7−1.1, (m, 24H). ^{13}C NMR: δ 175, 91.8, 77.2, 62.1, 60.7, 53.3, (30.4, 30.3), (28.2, 28.1), 25.0, (22.3, 22.2), 21.7. IR (film): ν 1747 cm^{-1}. HRMS (FAB): m/z calculated for $C_{21}H_{37}N_4O_4$ (M + 1) 409.2815, found 409.2804.

Bis(azapenam) 5b. Into a dry pressure tube was placed 745 mg (1.3 mmol) of bis(carbene) **2b**, 593 mg (2.6 mmol) of imidazoline **3**, and 130 mL of dry CH_2Cl_2. This mixture was degassed using the freeze−pump−thaw method three times. It was then flushed with CO (80 psi) three times and irradiated (450 W Conrad-Honovia 7825 medium-pressure mercury lamps with a Pyrex well) until the yellow color had faded (about 24 h). The solvent was removed, and the residue was dissolved into methanol and placed into the freezer. The $Cr(CO)_6$ was removed by filtration, and the solvent was removed under reduced pressure. This residue was dissolved in 1:1 hexane−ethyl acetate and exposed to air and sunlight (2 days or until clear). The solution was filtered, and the solvent was removed. Purification was accomplished on silica gel using 1:1 hexane−ethyl acetate to yield 379 mg (41%) of the N-protected bis(azapenam). The bis(azapenam) was dissolved in 25 mL of methanol, along with 190 mg of Pd/C (5%) and 25 drops of triethylamine. The tube was filled with 80 psi of H_2 and stirred for 1 h. The palladium was removed by filtration, and the solvent was removed to give 229 mg (0.54 mmol, 92%) of a white solid. ^{1}H NMR: δ 4.7 (s, 2H), 3.4 (s, 6H), 3.06, (d, J = 11 Hz, 4H), 2.66, (d, J = 11 Hz, 4H), 2.2 (s, 2H), 1.6−1.1 (m, 24 H). ^{13}C NMR: δ 175, 91.9, 77.2, 57.7, 56.2, 48.9, 25.4, 23.9, 20.5, 18.0, 17.4. IR (film): ν 1747, 1731 cm^{-1}. HRMS (FAB): m/z calculated for $C_{22}H_{39}N_4O_4$ (M + 1) 423.2971, found 423.2962.

Bis(azapenam) 5c. Azapenam **5c** was synthesized using the exact method as for **5a**, starting with 0.548 g (0.99 mmol) of **2b**, 0.519 g (1.88 mmol) of **4**, and 33 mL of CH_2Cl_2 to yield 0.326 g (0.42 mmol, 42%) of product. The protecting group was hydrogenated in the same way as for **5a**, starting with 0.326 g (0.42 mmol) of bis(azapenam), 160 mg of Pd/C (5%), 20 drops of triethylamine, and 20 mL of MeOH to yield 0.203 g (0.40 mmol, 95%) of a white solid. ^{1}H NMR: δ 4.86 (s, 2H), 3.77 (s, 6H), 3.69 (d, J = 12 Hz, 2H), 3.50 (s, 6H), 2.74 (d, J = 12 Hz, 2H), 1.78 (s, 6H), 1.7−1.3 (m, 14H). ^{13}C NMR: δ 174.6, 171.9, 92.2, 79.2, 65.9, 60.7, 53.4, 52.6, 29.7, 28.2, 22.3, 17.2. IR (film): ν 1754, 1736 cm^{-1}. HRMS (FAB): m/z calculated for $C_{24}H_{39}N_4O_8$ (M + 1) 511.2768, found 511.2752.

Bis(dioxotetraazacyclotetradecadiene) 6a. The bis-(azapenam) **5a** (0.202 g, 0.50 mmol) was dissolved in 60 mL of dry CH_2Cl_2. To this was added 70 mg of racemic camphorsulfonic acid, and the solution was stirred at room temperature for 5 days. The organic layer was washed one time with 50 mL of 5% $NaHCO_3$ (aqueous). This aqueous layer was extracted with 2 × 20 mL of CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and filtered, and the solvent was removed. The residue was purified by column chromatography using basic alumina and 98:2 CH_2Cl_2−CH_3OH to yield 81 mg (0.10 mmol, 35%) of the product as a white solid. ^{1}H NMR (CD_2Cl_2): δ (9.75, 9.0) (s, 4H), 7.65−7.55 (m, 4H), 4.65 (m, 4H), 3.4−3.2 (m, 16H), 2.2−1.0 (m, 44H). ^{13}C NMR (CD_2Cl_2): δ 169.6, 167.9, 82.5, 71.3, 37.6, 30.8, 25.4, (23.9, 23.7). IR (film):

(14) Bao, J.; Wulff, W. D.; Dominy, J. B.; Fumo, M. J.; Grant, E. B.; Rob, A. C.; Whitcomb, M. C.; Yeuna, S.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 3392.

(15) Beard, C. D.; Baum, K.; Grakanskus, V. *J. Org. Chem.* **1973**, *38*, 3673.

ν 1676, 1557 cm^{-1}. HRMS (FAB): *m*/*z* calculated for $C_{42}H_{73}N_8O_8$ (M + 1) 817.5551, found 817.5537.

Bis(dioxotetraazacyclotetradecadiene) 6b. Bis(dioxotetraazacyclotetradecadiene) **6b** was synthesized according to the procedure for **6a**, starting with 229 mg (0.54 mmol) of **5b**, 30 mg of camphorsulfonic acid, and 50 mL of CH_2Cl_2 to yield 83 mg (0.10 mmol, 41%) of the product. ^{1}H NMR: δ (9.87, 9.86) (s, 4H), (7.71, 7.70) (s, 4H), 3.58 (d, J = 13 Hz, 4H), 3.3−3.2 (m, 16H), 1.8−1.1 (m, 48H). ^{13}C NMR (CD_2Cl_2): δ 170, 168, 83.4, 70.9, 54.1, 39.1, 30.2, 25.7, 23.70, 23.66. IR (film): ν 1681, 1555, cm^{-1}. HRMS (FAB): *m*/*z* calculated for $C_{44}H_{77}N_8O_8$ (M + 1) 845.5864, found 845.5850.

Bis(dioxotetraazacyclotetradecadiene) 6c. Bis(dioxotetraazacyclotetradecadiene) **6c** was synthesized according to the procedure for **6a**, starting with 0.165 g (0.32 mmol) of azapenam **5c**, 20 mg of camphorsulfonic acid, and 35 mL of CH_2Cl_2 to yield 80 mg (0.08 mmol, 48%) of the product. ^{1}H NMR: δ 9.6 (s, 4H), 7.7 (s, 4H), 4.2−3.6 (m,20H), 3.4−3.2 (m, 12H), 2.0−1.1 (m, 36H). ^{13}C NMR: δ 172.1, 169.3, 168.7, 83.0, 60.3, 52.7, 51.5, 36.4, 34.0, 28.6, 24.8, 21.2. IR (film) ν 1741, 1680, 1516 cm^{-1}. HRMS (FAB): *m*/*z* calculated for $C_{48}H_{77}N_8O_{16}$ (M + 1) 1021.5458, found 1021.5452.

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