Remarkable high-yielding chemical modification of gold nanoparticles using uncatalyzed click-type 1,3-dipolar cycloaddition chemistry and hyperbaric conditions

Hossein Ismaili, Abdolhamid Alizadeh, Kristen E. Snell, and Mark S. Workentin

Abstract: Azide-terminated alkyl thiolate monolayer-protected gold nanoparticles (**1**-C_{12}MPN) with a core size of 1.8 ± 0.2 nm were prepared. **1**-C_{12}MPN was modified in high yields via an uncatalyzed 1,3-dipolar cycloaddition (click-type reaction) with a variety of terminal acyl–alkynes under hyperbaric conditions at 11 000 atm. The resulting 1,2,3-triazole modified MPNs (**2**-C_{12}MPN) were characterized using ^{1}H NMR spectroscopy and were verified by comparison of the spectra to those obtained for the products of the model reactions of 1-azidododecane with the same alkynes. TEM analysis showed that the high-pressure conditions did not affect the size of the gold core, suggesting that the only effect is to facilitate the chemical reaction on the particles.

Key words: nanoparticles, hyperbaric chemistry, 1,3-dipolar cycloaddition, monolayers.

Résumé : On a préparé des nanoparticules d'or protégées par une monocouche d'alkylthiol (**1**-C_{12}MPN) portant une fonction azide en position terminale et dont le diamètre principal est égal à 1,8 ± 0,2 nm. Le produit **1**-C_{12}MPN a été modifié avec des rendements élevés par le biais d'une cycloaddition 1,3-dipolaire non catalysée (réaction de type par un clic) avec une variété d'acyl–alcynes terminales, dans des conditions hyperbariques, à 11,000 atmosphères. Les nanoparticules d'or modifiées, protégées par une monocouche d'alkylthiol (**2**-C_{12}MPN) et portant un cycle 1,2,3-triazole ont été caractérisées par spectroscopie RMN du ^{1}H et ont été vérifiées par comparaison avec les spectres obtenus pour les produits des réactions modèles du 1-azidodécane avec les mêmes alcynes. Une analyse par microscopie électronique à transmission (MET) a permis de montrer que les conditions de haute pression n'ont pas affecté la taille du diamètre principal de l'or suggérant que le seul effet est de faciliter la réaction chimique sur les particules.

Mots-clés : nanoparticules, chimie hyperbarique, cycloaddition 1,3-dipolaire, monocouches.

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Introduction

The Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition of azides to terminal alkynes to produce a triazole ring, the "click" reaction, is a popular and powerful tool in organic synthesis and combinatorial chemistry.[1] This reaction is also being exploited in material science applications for the modification of metal and silica surfaces,[2] dendrimers,[3] and polymers.[4] Recently, the reaction was extended to monolayer-protected CdSe,[5] iron oxide,[6] and monolayer-protected gold nanoparticles (MPN).[7–12] Because the 1,3-dipolar cycloaddition reaction of an alkyne and azide is slow, this type of reaction is typically done in the presence of a Cu(I) catalyst because it facilitates the rapid, high reaction conversions with little or no byproducts under mild conditions. The later is of key importance for the functionalization of Au-MPN. While the catalyzed reaction is effective for the modification of the CdSe and iron oxide nanoparticles, this approach is not considered as feasible with gold nanoparticles. Gold MPNs (now simply referred to as MPNs) in the presence of the Cu catalyst have been suggested to be unstable, and lead to aggregation or decomposition likely due to the reaction of the Cu catalyst with the gold surface. In another case, Brennan et al. reported using the Cu-catalyzed route to modifiy azide-functionalized 12 nm MPNs with alkyne-appended lipases but a million-fold excess of Cu was required and the yield was less than 1% conversion.[7] More recently, and while this work was in progress, Astruc and co-workers reported specific reaction conditions to circumvent the difficulties of the Cu(I) click reaction on azide-terminated MPNs.[13]

Williams and co-workers reported a thorough study showing that the Huisgen dipolar cycloaddition reaction can be used to modify azide-terminated MPNs with a variety of activated alkynes without a catalyst.[8] However, the yields (extent of conversion of the azide groups) were extremely low (13% and less after 60 h in dioxane, depending on the alkyne) and could only be marginally improved by altering the solvent. In a latter study where they reported on the kinetics of this reaction on the MPN, they stated that these

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yields were slightly underestimated because of the method used to follow reaction conversion.[9] However, the yields were still relatively low (22%, or 54% in one specific case) and did not allow the product MPNs to be completely characterized by NMR spectroscopy. Because of the potential of this type of reaction as a general approach to surface modification and to allow the introduction of a variety of functionalities from common starting MPNs, an important goal is to improve the efficiency of this type of reaction on MPN. To this end, and while this work was in progress, Sommer and Weck reported on the microwave-assisted catalyzed 1,3-dipolar cycloaddition of azide-terminated MPNs.[10] The method proved successful and allowed a large variety of terminal alkynes to form triazole-functionalized MPN with near-quantitative yields, but still required very careful control of the microwave conditions because excess heating of the MPN lead to nanoparticle decomposition ascribed to particle aggregation.

Recently, we reported that the inefficient modification of a maleimide-modified MPN by the Diels–Alder reaction at ambient conditions with a series of dienes was improved remarkably using hyperbaric conditions without affecting the particle core.[14] The hyberbaric method for modification of gold MPNs was more general and was further used to accelerate the 1,3-cycloaddition of a large variety of nitrones to the maleimide-modified MPN in quantitative yields.[15] In both these studies, we showed that the reactions carried out on the MPNs at ambient temperature and pressure were significantly slower than the corresponding reactions on model compounds under the same conditions. We attributed this difference in reactivity to the unique steric effects of the environment at the interfacial site of reactivity on the MPN. In the present report, we extend this methodology to study the Huisgen 1,3-dipolar cycloaddition of azide-terminated MPN to terminal alkynes to improve the efficiency of this reaction and to expand the scope of reactions that can be utilized for modification of nanoparticles using hyperbaric conditions. The Huisgen 1,3-dipolar cycloaddition of azides to terminal alkynes is also subject to rate acceleration at elevated pressure, although as far as we are aware, this has only been the subject of one report.[16] Specifically, we report herein that azide-terminated, 1.8 nm core size MPNs prepared to be essentially identical to the original report of Williams and co-workers,[8] will react with activated acyl–alkynes efficiently under high-pressure conditions at ambient temperature to form the 1,2,3-triazoles essentially quantitatively in the absence of a Cu catalyst. This approach eliminates the complications due to the presence of catalysts or higher temperatures.

Experimental

Commercial solvents and reagents used

The compounds dodecanethiol, hydrogen tetrachloroaurate (III), tetraoctylammonium bromide, 1,12-dibromododecane, 11-bromo-1-undecene, azobis(isobutyronitrile) (AIBN), 1-bromododecane, sodium azide, ethynyl magnesium bromide, 1-octyn-3-ol, and ethyl propionate were all purchased from Aldrich and used as received. Deuterated benzene (C_6D_6), deuterated chloroform ($CDCl_3$), and deuterated dichloromethane (CD_2Cl_2) (Cambridge Isotope Laboratories) were also used as received.

General instrumentation

High-pressure reactions were carried out utilizing a LECO Tempres High-Pressure chemical reactor, which operates at 11 000 atm. ^{1}H and ^{13}C NMR spectra were recorded, as indicated, on either a Varian Inova 600 (^{1}H: 600 MHz, ^{13}C: 150 MHz) or 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometers and were referenced to the residual protons in the solvent relative to $(CH_3)_4Si$ (δ (ppm): chloroform-*d*, 7.26; dichloromethane-d_2, 5.32; or benzene-d_6, 7.15). Mass spectra and exact mass were recorded on a MAT 8200 Finnigan High resolution Mass Spectrometer. Infrared spectra were recorded on a Bruker Vector 33 FTIR spectrometer and are reported in wavenumbers (cm^{-1}). Melting points were measured using the Electrothermal 9100 melting-point instrument and are uncorrected. High resolution transmission electron microscopy (HRTEM) images were collected on a JEOL 2010F HRTEM.

Synthetic details

Dodecanethiolate MPN (C_{12}MPN)

Following the procedures of Brust–Shiffrin and Murray,[17,18] hydrogen tetrachloroaurate (III) trihydrate (0.30 g, 0.77 mmol) was dissolved in 28 mL distilled water (resulting in a bright yellow solution) and then mixed with tetraoctylammonium bromide (2.30 g, 4.2 mmol) in 70 mL toluene. The contents were stirred for 30 min at room temperature to facilitate the phase transfer of the hydrogen tetrachloroaurate (III) trihydrate into the toluene layer, which resulted in the organic layer turning to a dark orange colour and the aqueous layer becoming clear and colourless. After phase transfer, the aqueous layer was removed and the organic layer was cooled to 0 °C in ice bath. Dodecanethiol (0.468 g, 0.57 mL, 2.31 mmol) was added to the solution via a volumetric pipette and allowed to stir for 10 min. The addition of dodecanethiol resulted in a colour change from brownish-orange to clear and colourless. A fresh solution of sodium borohydride (0.33 g, 8.7 mmol) in 28 mL water was then added to the rapidly stirring toluene solution over 5 s. The solution darkened instantly, eventually becoming dark brown. The mixture was allowed to stir overnight (~18 h) as it warmed to room temperature, after which time, the aqueous layer was removed and the toluene layer was washed with 3 × 20 mL distilled water and dried over $MgSO_4$. The toluene layer was then isolated by gravity filtration and evaporated to dryness. The resulting mixture of C_{12}MPN and tetraoctylammonium bromide was suspended in 200 mL of 95% ethanol and placed in the freezer overnight during which time the C_{12}MPN precipitated from solution. When the MPN had precipitated, the supernatant was decanted and the precipitate was dissolved in benzene and concentrated, resulting in the formation of a film in the round-bottom flask. This film was washed repeatedly with 10 × 15 mL of 95% ethanol, resulting in pure C_{12}MPN as judged by ^{1}H NMR spectroscopy, which showed no signs of free dodecanethiol, dodecyldisulfide, or tetraoctylammonium bromide. The resulting C_{12}MPN was dark brown.

Synthesis of bromo-terminated C_{12}MPN

Approximately 200 mg of C_{12}MPN was dissolved in 60 mL of benzene and degassed with nitrogen. 290 mg

(1.54 mmol) of 11-bromo-1-undecanethiol was added to the solution and stirred for 2 days at room temperature. The mixture was then concentrated and the resulting film was washed with 95% ethanol and dried. The ^{1}H NMR spectrum of this MPN is shown in Fig. S1. ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 3.4, 1.9, 1.8–1.0, 0.9. The integrated areas of methylene protons alpha to the bromide and terminal methyl group of dodecanethiolate in the ^{1}H NMR spectra reveals that the ratio of ligands on the bromoundecane-thiolate-modified C_{12}MPN was 1:1.2, terminal bromide to terminal methyl.

The required 11-bromo-1-undecanethiol was synthesized by the reported method.[19] 11-Bromo-1-undecene (1.5 g, 6.43 mmol), AIBN (0.6 g, 3.65 mmol), and thioacetic acid (3 mL) were dissolved in toluene and refluxed for 2 h. The reaction mixture was washed with water and then concentrated. The crude product was purified by column chromatography (eluting with 5:1 hexanes/ethyl acetate) to separate. A solution of 11-bromo-1-undecanethioacetate in dry methanol was cooled in an ice bath, then 3 mL acetyl chloride was added dropwise, and the solution was stirred for 6 h at room temperature. The reaction was quenched by adding water and extracted with CH_2Cl_2, and then combined extracts were washed with water. The organic layer was dried over $MgSO_4$ and evaporated to get the pure product: Yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.40 (t, J = 6.8 Hz, 2H), 2.51 (q, J = 7.3 Hz, 2H), 1.84 (m, 2H), 1.60 (m, 2H), 1.44–1.27 (m, 15H).

Synthesis of azide-terminated MPN: (1-C_{12}MPN)

1-C_{12}MPN was prepared according to the procedure of Fleming et al.[8] A 60 mL solution of 0.25 mol/L NaN_3 in DMSO was added to the mixture of the bromo-terminated MPN (prepared as above) in benzene (~200 mg of bromo-terminated C_{12}MPN in 60 mL of benzene) and the mixture was stirred for 48 h. After which time, the reaction was quenched with water and organic layer was separated and washed with water three times, dried over $MgSO_4$, and then concentrated. The resulting film was rinsed with 95% ethanol and dried. ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 3.4, 3.25, 1.9, 1.85–1.0, 0.9. The ^{1}H NMR spectrum of this **1**-C_{12}MPN is shown in Fig. 1*a*. The integrated areas of the three types of ligands, determined by decomposition of 10 mg of **1**-C_{12}MPN with ~2 mg of iodine, showed that the ratio of terminal azide/bromide/methyl was 3.5:1:5. Additionally, **1**-C_{12}MPN was characterized using IR spectroscopy and TEM. IR (cm^{-1}): 2959, 2921, 2853, 2096, 1467, 1366, 1282, 1089, 1040, 801. The average particle size was determined by analysis of TEM images of numerous samples: 1.8 ± 0.2 nm

Synthesis of 1-azidododecane (3)

A solution of 1-bromododecane (2 g, 8 mmol) and NaN_3 (0.57 g, 8.8 mmol) in DMSO (30 mL) was stirred overnight at room temperature. The reaction mixture was diluted with diethyl ether and washed with water five times to remove DMSO. The ethereal layer was dried over $MgSO_4$ and concentrated. The spectral data are in accord with the literature.[20] Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.25 (t, J = 6.9 Hz, 2H), 1.59 (m, 2H), 1.37–1.26 (broad, 18H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 51.7, 32.1, 29.8, 29.77, 29.71, 29.5, 29.4, 29.0, 26.9, 22.9, 14.3. IR (cm^{-1}): 2955, 2924, 2854, 2095, 1467, 1366, 1258.

Synthesis of alkynes (4a–4i)

Compounds 1-pyren-1-yl-propyn-1-one (**4a**), 1-anthracen-9-yl-propyn-1-one (**4c**), propynoic acid phenylamide (**4h**),[8] 1-ferrocenyl-2-propyn-1-one (**4b**),[21] and 1-(4-nitrophenyl)-2-propyn-1-one (**4e**)[22] were prepared by their literature method, and their ^{1}H NMR spectra are in accord with those reported. Compounds 1-phenyl-2-propyn-1-one (**4f**), 1-(4-biphenyl)-2-propyn-1-one (**4d**), and 1-octyn-3-one (**4i**),[23] as well as 1-(2-methylphenyl)-2-propyn-1-one (**4g**),[24] were synthesized by the following procedure (except for **4i** where commercial alcohol was oxidized by magnesium(IV) oxide), and their ^{1}H NMR spectra are in accord with those reported: 5 mmol of the corresponding aldehyde was dissolve in 10 mL of THF and cooled in an ice bath. 10 mL of ethynyl magnesium bromide (0.5 mol/L in THF) was added dropwise in 15 min. The mixture was allowed to stir for 3 h as it warmed to room temperature, after which time, the reaction was quenched with saturated NH_4Cl and extracted with ether. Organic layer was dried over $MgSO_4$ and then concentrated. The crude product was purified by column chromatography (eluting with 3:1 hexanes/ethyl acetate).The corresponding alcohol was dissolved in 10 mL CH_2Cl_2 and 5.2 g (60 mmol) of magnesium(IV) oxide was added and the mixture was stirred at room temperature for 1 h. The oxidized reagent was removed by filtration through Celite, the organic layer was washed with water (three times), and the solvent was evaporated.

General procedures for azide–alkyne Huisgen 1,3-dipolar cycloaddition reactions at high-pressure conditions

Preparation of 2-C_{12}MPN

Approximately 10 mg of **1**-C_{12}MPN was dissolved in ~2.0 mL of CH_2Cl_2 then mixed with 15–20 equiv. of the appropriate activated acyl–alkynes (**4a**–**4j**). The mixture was transferred into a brass-clamp-sealed PTFE tube and placed in the LECO Tempres High-Pressure reactor at 11 000 atm for 15–24 h. The product **2a**–**2j**-C_{12}MPNs were purified by washing with 95% ethanol and then CH_3CN to remove any unreacted alkyne. IR and ^{1}H NMR spectroscopy were used to check the completion of the reaction, as described below, and purity of the resulting **2a**–**2j**-C_{12}MPNs. The NMR spectra obtained were compared to those of the products of the model reaction, **5a**–**5j**. These are provided, along with IR spectra in the Supporting information.

2a-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.63–7.73, 4.28, 3.40. IR (cm^{-1}, dropcast on NaCl): 2921, 2851, 1643, 1467, 1225, 923, 849, 805, 716.

2b-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.23, 5.49, 4.95, 4.63, 4.42, 4.14, 3.66, 3.41, 3.25, 1.9–0.88. IR (cm^{-1}, dropcast on NaCl): 2925, 2853, 2096, 1631, 1530, 1453, 1260, 1039, 825, 721.

2c-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.58, 8.04, 7.73, 7.39, 4.16, 3.40, 1.70–0.86 IR (cm^{-1}, dropcast on NaCl): 2962, 2921, 2851, 1678, 1467, 1261, 1095, 1019, 805.

2d-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.45–8.30, 7.67–7.42, 4.41, 3.40, 1.94–0.87. IR (cm^{-1}, dropcast on

NaCl): 2961, 2922, 2851, 1652, 1603, 1458, 1261, 1092, 1056, 906, 801, 749.

2e-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.58, 8.33, 4.45, 3.40, 1.97–0.87. IR (cm^{-1}, dropcast on NaCl): 2960, 2920, 2851, 1653, 1525, 1343, 1261, 1093, 1041, 848, 798.

2f-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.34, 7.59–7.46, 4.40, 3.40, 1.90–0.87. IR (cm^{-1}, dropcast on NaCl): 2964, 2924, 2854, 1653, 1603, 1457, 1261, 1115, 1019, 904, 815, 698.

2g-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.18, 7.67, 7.38–7.26, 4.36, 3.38, 2.38, 1.89–0.87. IR (cm^{-1}, dropcast on NaCl): 2918, 2849, 2075, 1657, 1524, 1457, 1228, 1015, 904, 798, 742.

2h-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 9.09, 8.24, 7.71, 7.33, 7.13, 4.36, 3.41, 1.86–0.87. IR (cm^{-1}, dropcast on NaCl): 2961, 2921, 2851, 2094, 1678, 1599, 1467, 1260, 1087, 1036, 797.

2i-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.18, 4.33, 3.37, 1.87–0.87. IR (cm^{-1}, dropcast on NaCl): 2955, 2921, 2852, 1739, 1437, 1260, 1224, 1199, 1108, 1039, 800, 721.

2j-C_{12}MPN: ^{1}H NMR (600 MHz, CD_2Cl_2) δ: 8.15, 4.39, 3.40, 3.25, 3.06, 1.92–0.89. IR (cm^{-1}, dropcast on NaCl): 2922, 2852, 2091, 1691, 1468, 1261, 1224, 798, 723.

Preparation of 5a–5j

Alkynes (**4a**–**4j**) (0.15 mmol) and 1-azidododecane (**3**) (0.16 mmol) were dissolved in ~2 mL of CH_2Cl_2 then transferred into a brass-clamp-sealed PTFE tube and placed in the LECO Tempres High-Pressure reactor at 11 000 atm and room temperature for 10 h. The product was removed from unreacted alkyne by preparative TLC plate (3:1 hexanes/ethyl acetate). The resulting products, **5a**–**5j**, were characterized as summarized below.

5a: Yellow solid, mp 81–84 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.61 (d, *J* = 9.3 Hz, 1H), 8.32–8.30 (m, 2H), 8.25–8.20 (m, 4H), 8.15–8.10 (m, 2H), 7.81 (s, 1H), 4.93 (t, *J* = 7.4 Hz, 2H), 2.10–2.04 (m, 2H), 1.49–1.37 (m, 4H), 1.32–1.25 (broad, 14 H), 0.87 (t, *J* = 7.0, 3H). ^{13}C NMR ($CDCl_3$) δ: 14.1, 22.7, 26.6, 29.1, 29.3, 29.4, 29.5, 29.6, 30.5, 31.9, 50.9, 123.8, 123.9, 124.1, 124.8, 126.5, 126.6, 126.7, 126.9, 127.1, 127.2, 127.3, 130.0, 130.2, 130.9, 131.1, 132.1, 134.3, 140.4, 186.0. IR (cm^{-1}, dropcast on NaCl): 3240, 2923, 2853, 1650, 1510, 1221, 999, 926, 849, 708. MS (EI): Exact mass ($C_{31}H_{35}N_3O$) calcd.: 465.2780, found: 465.2777.

5b: Maroon oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (s, 1H), 5.52–5.51 (m, 2H), 4.65–4.64 (m, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 4.17 (s, 5H), 2.00–1.93 (m, 2H), 1.35–1.25 (broad, 18H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.4, 28.9, 29.3, 29.4, 29.5, 29.6, 30.1, 31.9, 50.5, 70.2, 71.6, 73.0, 126.3, 149.1, 189.2. IR (cm^{-1}, dropcast on NaCl): 3117, 2925, 2853, 1629, 1528, 1444, 1377, 1260, 1107, 1041, 826, 771. MS (EI): Exact mass ($C_{25}H_{35}N_3FeO$) calcd.: 449.2129, found: 449.2139.

5c: Yellow solid, mp 84–86 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.97 (s, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.47 (t, 2H), 7.42 (t, 2H), 4.35(t, *J* = 7.3 Hz, 2H), 1.92–1.87 (m, 2H), 1.31–1.24 (broad, 18H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.4, 28.9, 29.3, 29.4, 29.5, 29.6, 30.1, 31.9, 50.7, 125.0, 125.4.3, 126.6, 127.4, 128.5, 128.7, 129.1, 131.1, 133.4, 149.0, 192.0. IR (cm^{-1}, dropcast on NaCl): 3132, 3056, 2920, 2852, 1653, 1525, 1470, 1180, 884, 841, 729. MS (EI): Exact mass ($C_{29}H_{35}N_3O$) calcd.: 441.2780, found: 441.2783.

5d: Yellow solid, mp 94–98 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.55 (d, *J* = 8.2 Hz, 2H), 8.27 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 7.4 Hz, 2H), 7.48 (t, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 4.45(t, *J* = 7.2 Hz, 2H), 2.00–1.95 (m, 2H), 1.37–1.25 (broad, 18H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.1, 22.6, 26.4, 28.9, 29.2, 29.3, 29.4, 29.5, 30.1, 31.9, 50.8, 127.0, 127.3, 128.1, 128.2, 128.9, 131.2, 135.3, 140.0, 145.8, 148.2, 185.2. IR (cm^{-1}, dropcast on NaCl): 3126, 2918, 2848, 1633, 1602, 1523, 1467, 1344, 1255, 909, 876, 851, 746, 692. MS (EI): Exact mass ($C_{27}H_{35}N_3O$) calcd.: 417.2780, found: 417.2787.

5e: Yellow solid, mp 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (d, *J* = 9.0 Hz, 2H), 8.35 (d, *J* = 9.0 Hz, 2H), 8.32 (s, 1H), 4.46 (t, *J* = 7.2 Hz, 2H), 2.01–1.94 (m, 2H), 1.35–1.24 (broad, 18H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.4, 28.9, 29.2, 29.3, 29.4, 29.5, 30.1, 31.8, 50.8, 123.4, 128.5, 131.6, 141.2, 147.4, 150.3, 183.8. IR (cm^{-1}, dropcast on NaCl): 3129, 2915, 2849, 1643, 1599, 1518, 1331, 1237, 1047, 1016, 911, 881, 847, 785, 725, 694. MS (EI): Exact mass ($C_{21}H_{30}N_4O_3$) calcd.: 386.2317; found: 386.2320.

5f: Yellow solid, mp 49–51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (d, *J* = 8.7 Hz, 2H), 8.25(s, 1H), 7.61 (t, 1H), 7.51 (t, 2H), 4.44 (t, *J* = 7.2 Hz, 2H), 1.99–1.92 (m, 2H), 1.34–1.24 (broad, 18H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.4, 28.9, 29.2, 29.3, 29.4, 29.5, 30.1, 31.8, 50.6, 128.1, 128.4, 130.6, 133.2, 136.5, 148.0, 185.7. IR (cm^{-1}, dropcast on NaCl): 3137, 2957, 2853, 1653, 1577, 1260, 1234, 1181, 1045, 1018, 904, 798, 725, 696. MS (EI): Exact mass ($C_{21}H_{31}N_3O$) calcd.: 341.2467; found: 341.2477.

5g: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.31–7.28 (m, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 2.45(s, 3H), 1.98–1.91 (m, 2H), 1.33–1.25 (broad, 18H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 20.3, 22.6, 26.4, 28.9, 29.2, 29.3, 29.4, 29.5, 30.1, 31.8, 50.6, 125.2, 127.5, 130.1, 131.2, 131.3, 137.1, 137.9, 148.3, 189.5. IR (cm^{-1}, dropcast on NaCl): 3135, 2925, 2855, 1658, 1524, 1460, 1440, 1233, 1042, 905, 742 MS (EI): Exact mass ($C_{22}H_{33}N_3O$) calcd.: 355.2623, found: 355.2614.

5h: Yellow solid, mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (s, 1H), 8.13 (s, 1H), 7.69 (*J* = 7.6 Hz, 2H), 7.38 (t, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 4.42 (t, *J* = 7.2 Hz, 2H), 1.98–1.92 (m, 2H), 1.33–1.25 (broad, 18H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.4, 28.9, 29.3, 29.34, 29.5, 29.6, 30.1, 31.9, 50.9, 119.8, 124.5, 125.5, 129.1, 137.5, 143.4, 163.9. IR (cm^{-1}, dropcast on NaCl): 3317, 3139, 2920, 2851, 1664, 1558, 1437, 1047, 800, 749, 689. MS (EI): Exact mass ($C_{21}H_{32}N_4O$) calcd.: 356.2576, found: 356.2589.

5i: Colourless solid, mp 80–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (s, 1H), 4.39 (t, *J* = 7.2 Hz, 2H), 3.11 (t, *J* = 7.5 Hz, 2H), 1.95–1.88 (m, 2H), 1.78–1.71 (m 2H), 1.40–1.24(broad, 22H), 0.92–0.86 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.1 22.5, 22.7, 23.7, 26.4, 28.9, 29.31, 29.33, 29.5, 29.6, 30.1, 31.5, 31.9, 39.5, 50.6, 125.1, 148.1,

195.7. IR (cm^{-1}, dropcast on NaCl): 3102, 2915, 2847, 1687, 1469, 1241, 1159, 1055, 970, 887, 719. MS (EI): Exact mass ($C_{20}H_{37}N_3O$) calcd.: 335.2936, found: 335.3001.

5j: Colourless oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 4.70 (t, J = 7.4 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.94–1.84 (m, 2H), 1.39 (t, J = 7.1 Hz, 2H), 1.31–1.24 (broad, 18H), 0.87 (t, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 14. 14, 22.7, 26.4, 29.0, 29.3, 29.4, 29.5, 29.6, 30.3, 31.9, 50.4, 61.7, 127.7, 137.9, 158.5. IR (cm^{-1}, dropcast on NaCl): 2956, 2855, 1731, 1528, 1457, 1311, 1255, 1092, 772. MS (EI): Exact mass ($C_{17}H_{32}N_3O_2$) ($M+H^+$) calcd.: 310.2494, found: 310.2482.

Results and discussion

The azide-terminated MPNs were prepared according to the method recently reported.[8] Starting with 1.8 ± 0.2 nm dodecanethiol-stabilized MPN (C_{12}-MPN), 11-bromoundecanethiol was introduced onto the MPN using the place-exchange method to yield a mixed monolayer containing Br-terminated undecanethiol ligands. Reaction of this MPN with NaN_3 in DMSO introduced the azide functionality onto the MPN. The ratio of terminal azide/bromide/methyl in the newly made mixed MPN was estimated to be roughly 3.5:1:5 by ^1H NMR spectroscopy of I_2-reduced MPNs. This mixed monolayer particle (**1**-C_{12}MPN) was further characterized by IR and UV–vis spectroscopy and TEM. Figure 1*a* shows the ^1H NMR spectrum of **1**-C_{12}MPN. The key diagnostic signals are the characteristically broad signals due to the methylene protons alpha to the azide and bromide functionality at 3.24 and 3.41 ppm, respectively. The IR spectrum of **1**-C_{12}-MPN also shows a strong absorbance at 2096 cm^{-1} due to the antisymmetric –N=N=N stretch in addition to the CH_2/CH_3 stretches at 2959, 2921, and 2852 cm^{-1}.

Compound **1**-C_{12}MPN (~10 mg) was then mixed with each of the activated acyl–alkynes **4a**–**4j**, shown in Scheme 1, in a ratio of 1:15–20 in 2 mL of CH_2Cl_2 and placed in a high-pressure reactor at 11 000 atm at ambient temperature. Model reactions of 1-azidododecane (**3**) with each alkyne were also performed under high-pressure conditions to aid in monitoring the extent of reaction and to provide analogous 1,2,3-triazole products (**5a**–**5j**) to allow for characterization of the reactions on **1**-C_{12}MPN (Scheme 2). The extent of reaction of **1**-C_{12}MPN was followed by ^1H NMR and IR spectroscopy. The reaction was considered complete when there was no evidence of the protons alpha to the azide in the ^1H NMR spectrum and by the disappearance of the azide peak in the IR spectrum. For most cases, this occurred after 15–24 h, depending on the alkyne (Table 1). We note that high temperatures cannot be employed to decrease reaction times for **1**-C_{12}MPN because MPNs are not thermally stable for extended periods. The reaction of **1**-C_{12}MPNs with alkynes **4a**, **4c**, **4d**, **4e**, and **4f**, resulting in the corresponding **2**-C_{12}MPNs, was quantitative after 15 h (perhaps less). Alkynes **4b**, **4g**, **4h**, **4i**, and **4j** had slightly lower 1,3-dipolar cycloaddition reactivity, and their reactions with **1**-C_{12}MPNs was carried out for 24 h. After which time, the azide peak in the IR spectra was completely absent for mixtures containing **4g**, **4h**, and **4j**, indicating near-complete conversion, but only around 80% conversion was observed for the reaction of the **1**-C_{12}MPNs with **4b** and **4i** (Table 1). Presumably, extending the reaction times further would lead to more complete conversion for these two less activated alkynes.

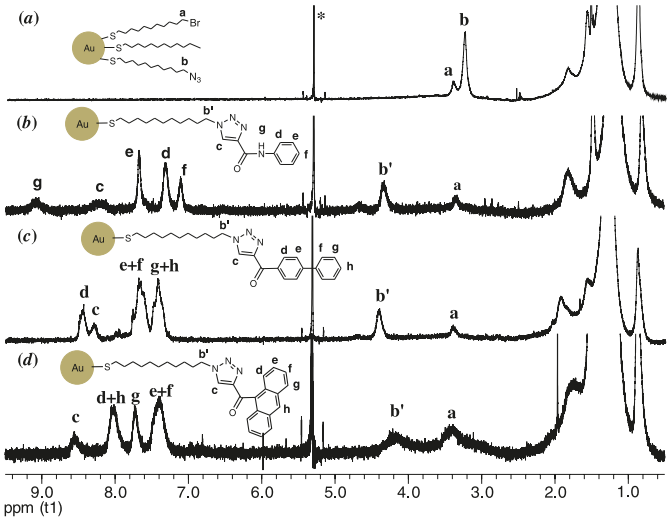
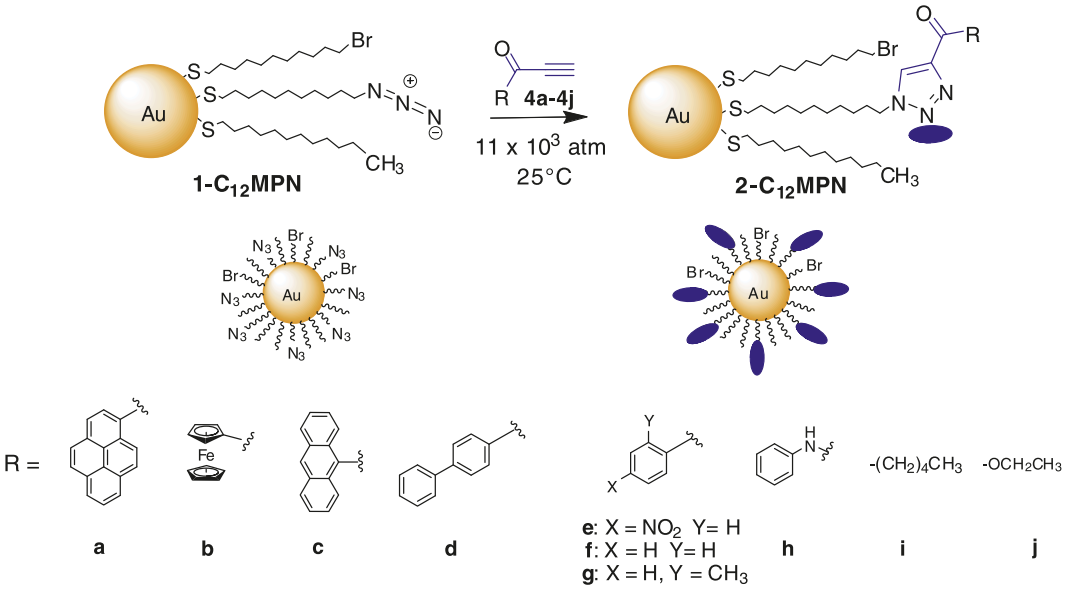


Fig. 1. ^1H NMR spectra of **1**-C_{12}MPN (*a*) and representative product 1,2,3-triazoles **2**-C_{12}MPN formed in click reactions of **1**-C_{12}MPN with acyl alkynes **4h**, **4d**, and **4c**: (*b*) **2h**-C_{12}MPN, (*c*) **2d**-C_{12}MPN, and (*d*) **2c**-C_{12}MPN. Solvent: CD_2Cl_2, residual proton signal is indicated by *.

After completion of the reaction and removal of the reaction mixture from the high-pressure reactor, the mixtures were washed several times to remove excess alkyne from the MPN and a ^1H NMR spectrum was recorded. These spectra show that **1**-C_{12}MPN had reacted to form the corresponding 1,2,3-triazole product **2**-C_{12}MPN. Figures 1*b*–1*d* show representative ^1H NMR spectra of the product **2**-C_{12}MPN formed by reaction of **1**-C_{12}MPN with alkynes **4h**, **4d**, and **4c**, respectively. Evidence for the reaction includes the downfield chemical shift of the protons alpha to the nitrogen atom from 3.24 ppm in the azide (labeled b) to ~4.2 ppm (labeled b′), alpha to the triazole ring (Fig. 1). The disappearance of the signal at 3.24 ppm on the **1**-C_{12}MPNs was considered as a sign of complete conversion of the azide. IR spectra of **2a**–**2j**-C_{12}MPN also show loss of the –N=N=N stretch at 2096 cm^{-1}, verifying completion of the reaction, and a new stretch at ~ 1639–1670 cm^{-1} due to the C=O (1734 cm^{-1} for ester **2j**-C_{12}MPN). Common to all spectra is the absence of the signal at 3.24 due to the CH_2 alpha to the azide, and a new signal appears between 7.8–8.6 ppm (chemical shift varies slightly with structure) due to the triazole C–H proton (labeled c in the spectra). Of course, other signals in the NMR spectra due to the functionality introduced with the cycloaddition with the alkyne are assignable easily by comparison to the spectra of the products of the model reactions, **5a**–**5j**. These are provided in the Supporting information. For example, The ^1H NMR spectra of **2h**-C_{12}MPNs (Fig. 1*b*) shows new peaks in the aromatic region attributed to the aromatic ring as well as the triazole C–H proton at 8.25 ppm and the amide proton at 9.15 ppm, verifying the formation of the triazole ring. It is noticeable that the ^1H NMR of the **2a**- and **2c**-C_{12}MPN with a relatively bulky R group (pyrene and anthracene) shows broad-

Scheme 1. The 1,3-dipolar cycloaddition of **1**-C_{12}MPN with a variety of terminal acyl-alkynes (**4a**–**4j**) at 11 000 atm.



Scheme 2. Model reaction of 1-azidododecane (**3**) with alkenes (**4a**–**4j**) to yield 1,2,3-triazoles (**5a**–**5j**).

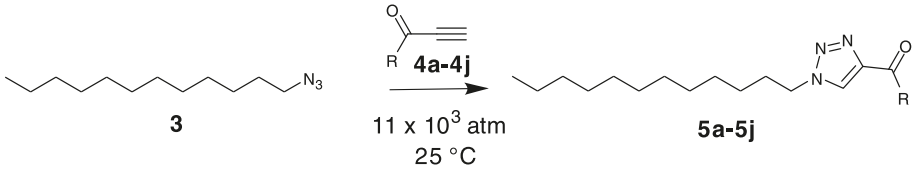


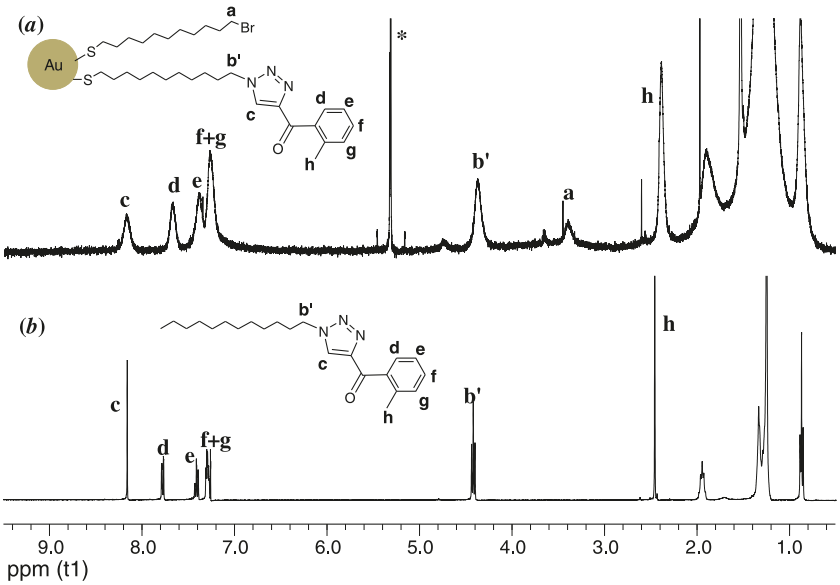
Table 1. Extent of reaction of **1**-C_{12}MPN with alkynes (**4a**–**4j**) via uncatalyzed 1,3-dipolar cycloaddition reaction at atmospheric and hyperbaric pressure conditions.

Alkyne	% Conversion (atmospheric pressure)[a]	% Conversion (11 000 atm)
4a	13	>95[c]
4b	12	>80[d]
4c	6	>95[c]
4d	6	>95[c]
4e	6	>95[c]
4f	NR[b]	>95[c]
4g	NR	>95[d]
4h	NR	>95[d]
4i	NR	>80[d]
4j	NR	>95[d]

[a]60 h in dioxane; see ref. 8.
[b]NR: Not reported.
[c]As determined by NMR after 15 h.
[d]As determined by NMR after 24 h.

ened peaks, especially for the peak assigned to the methylene group (b′) adjacent to the triazole ring, in comparison with the **2**-C_{12}MPNs with less-bulky R groups. This broadness suggests that the bulky group limits the mobility of these groups on the MPNs more than that of the less-bulky R groups. UV–vis spectra and TEM of the particles after reaction verify that there is no measureable change to the Au core size and that the only effect of the high-pressure conditions is the acceleration of the 1,3-dipolar cycloaddition. Although these reactions were only carried out at relatively small scale, they are easily scalable to the gram scale (or more) making the use of the hyperbaric reactor practical for synthetic preparations on MPNs. As mentioned above, to facilitate the assignment of the protons of the ^{1}H NMR spectra of **2**-C_{12}MPNs, the reactions were also carried out using the solution-phase reaction of 1-azidododecane with the same alkynes at high-pressure conditions as a model reaction to yield compounds **5a**–**5j** (Scheme 2). Compounds **5a**–**5j** could be characterized more completely via ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, as well as mass spectrometry (see Experimental). Because the ^{1}H NMR spectra of **5a**–**5j** are not as broad as those of **2**-C_{12}MPN, they are more easily assignable, and hence they provide the confidence in the assignments of the spectra for **2**-C_{12}MPN. For example, Fig. 2 shows the ^{1}H NMR spectra of **2g**-C_{12}MPN and the model compound **5g**, respectively. The signals at 4.4 ppm (b′), alpha to the triazole ring, and 8.18 ppm (c), attributed to the C–H proton of triazole ring, verify the formation of the cycloaddition product on the MPN. The other signals observed for **2g**-C_{12}MPN are also readily assignable because the intensity and chemical shift are comparable to **5g** except the expected broadening of the ^{1}H NMR signals on the MPN. The labeled ^{1}H NMR spectra of **2a**–**2j**-C_{12}MPN and the corresponding model compounds **5a**–**5j** are provided in the Supporting information. In general, the reaction of the 1-azidododecane with the less-electron-deficient dipolarophiles (**4d**, **4f**, and **4h**) provided a higher yield in the same reaction time compared with the more-electron-deficient (**4e** and **4j**) and the sterically hindered (**4a**–**4c**)

Fig. 2. ^{1}H NMR spectra of (*a*) **2g**-C_{12}MPN in CD_2Cl_2* and (*b*) compound **5g** in $CDCl_3$.



alkynes; a result mirrored in the reactivity of **1**-C_{12}MPN with the same alkynes (Table 1).

The Huisgen uncatalyzed 1,3-dipolar cycloaddition of an azide with an alkyne can lead to two possible regioisomers: the 1,4- (anti) and 1,5- (syn) isomers. Only the 1,4 isomer is shown as a product in Schemes 1 and 2. In cases where the alkyne is electron-defficient[25] or when a sterically bulky azide[26] is used, the 1,4-isomer is usually the major product (e.g., 1,3-dipolar cycloadditions of 1-azidoadamantane with ethyl propionates form only 1,4 isomers). The formation and ratio of the 1,4- and 1,5-isomers can be determined by ^{1}H NMR spectroscopy because the C–H triazole protons of the 1,4- and1,5-isomers are different, the latter usually downfield of the former. In this study, the ^{1}H NMR spectra of **2a**–**2j**-C_{12}MPNs show only one peak that can be assigned as a C–H proton of the triazole ring; this indicates that there is one major isomer formed. Because the alkynes used in this study are electron-deficient and the environment around the azide moiety in **1**-C_{12}MPN is sterically hindered, the formation of 1,4-isomer is the regioisomer that is most likely preferred.

The NMR and IR data together indicate the essentially quantitative conversion of the azide-terminated ligand **1**-C_{12}MPN to the corresponding 1,2,3-triazole **2a**–**2j**-C_{12}MPN under hyperbaric conditions. This can be compared to those of the reaction of the similarly azide-terminated MPN with a number of the same alkynes in the absence of a catalyst in dioxane for 60 h: **a** (13%), **b** (12%), **c** (6%), **e** (6%), and **h** (6%).[8] The use of high pressure leads to efficient and high-yielding chemical modification of monolayer-protected gold nanoparticles for this reaction system. We believe that the hyperbaric reaction method described here is general for performing this reaction with activated alkynes in the absence of catalyst. As such, it can be used as a preparative tool in performing these azide–alkyne 1,2-dipolar cycloadditions for the preparation of novel materials where high chemical conversion is desirable, where the use of the copper-based catalysts is problematic, or in applications where the toxicity of the Cu complicates purification.

Supplementary data

Supplementary data (^{1}H NMR spectra of the bromine-terminated-MPN, **1**-C_{12}MPN, ^{1}H NMR and IR spectra **2a**–**2j**-C_{12}MPN, and ^{1}H NMR spectra of **5a**–**5j**) for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5301. For more information on obtaining material, refer to cisti-icist.nrc-cnrc.gc.ca/cms/unpub_e.shtml.

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