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Chemical Modification of Monolayer-Protected Gold Nanoparticles Using Hyperbaric Conditions

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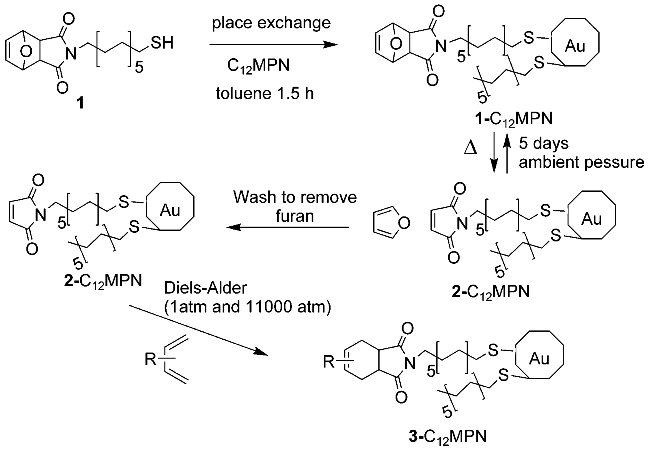
The ability to perform interfacial reactions on monolayer-protected gold nanoparticles (MPNs) to introduce new functionality is a key step for their use in applications. Such reactions may be important for altering the physical or chemical properties of the MPN or be the chemical recognition event itself.[1−7] Interfacial organic reactions in the MPN environment are often substantially different than the corresponding solution-phase reactions and for this reason cannot necessarily be used effectively to modify the MPN without first examining and understanding the factors that control the reaction.

The Diels−Alder reaction has been used effectively for the chemical modification of two-dimensional self-assembled monolayer (SAM) surfaces, especially on gold. The reaction has been used to explore fundamental physical organic interfacial reaction phenomena[8] and used practically for the immobilization of biological substrates onto the surfaces.[9,10] The use of the Diels−Alder reactions for modification of MPNs has not yet been examined in as much detail.[11,12] Recently we published a method to prepare a mixed maleimide−dodecanethiolate modified monolayer-protected gold nanoparticle (**2**-C_{12}MPN) and showed that it could serve as a dienophile and react with furan via a Diels−Alder reaction. Further, we demonstrated that **2**-C_{12}MPN reacts with a corresponding furan modified-MPN for the *reversible* assembly of a 3D network of MPNs.[12] This study relied on the well-known Diels−Alder reaction of maleimide with furan, which is reversible at slightly elevated temperatures.[13] While the reverse reaction on the MPN is rapid, a major drawback for the interfacial Diels−Alder reaction is that the forward process is very slow; in the case of the reaction of **2**-C_{12}MPN with a large excess of furan it took over 5 days at ambient conditions.

Recognizing that the Diels−Alder reaction is subject to rate acceleration under high pressure because of its negative volume of activation,[14] we report the interfacial Diels−Alder reaction of a **2**-C_{12}MPN with a series of dienes of varying steric and electronic demand under hyperbaric conditions. Reactions that did not proceed or proceeded only after days on the MPN at ambient temperature and pressure were completed in less than 10 min at 25 °C at 11000 atm, with no change in the gold core size. As far as we are aware the use of high pressure to accelerate reactions on metal surfaces is unprecedented; recently high-pressure was used to activate Diels−Alder reactions for the functionalization of single-wall carbon nanotubes.[15] The results here suggest that hyperbaric conditions offer a powerful route for interfacial chemical modification of organic-modified metal surfaces with appropriate reactions that are otherwise sluggish or impractical.

The **2**-C_{12}MPN was prepared using the method we recently reported.[12] Briefly, dodecanethiolate modified nanoparticles (C_{12}−MPN) were prepared using the Brust−Schiffrin method by mixing an organic solution of a 1:1 ratio of dodecanethiol/hydrogen tetrachloroaurate with TOAB and 10 fold excess of $NaBH_4$.[16] Next, the Diels−Alder protected furan−maleimide dodecyl thiol (**1**) was incorporated onto the C_{12}−MPN using the standard place-exchange method,[17] specifically using C_{12}−MPN/**1** in a 1:1.5 ratio (Scheme 1). Because maleimide reacts rapidly with thiols in a Michael-type reaction a 12-maleimide−dodecanethiol cannot be place-exchanged directly. Further, the mixed ligand MPN is prepared because the MPN containing only maleimide ligands has limited solubility in the solvents used. The maleimide containing MPN (**2**-C_{12}MPN) is liberated by heating the **1**-C_{12}MPN in toluene to initiate a retro-Diels−Alder reaction and releasing furan into solution. The furan was then washed away with 95% ethanol to leave **2**-C_{12}MPN. This protocol is used to prepare **2**-C_{12}MPN as needed, because **1**-C_{12}MPN is stable over long periods. The **2**-C_{12}MPN was characterized using ^{1}H NMR spectroscopy, which showed the absence of free furan, TEM (2.5 ± 0.5 nm), TGA (23% organic content), and IR spectroscopy. The ^{1}H NMR spectrum of **2**-C_{12}MPN, provided in the Supporting Information, shows the characteristic broad NMR signals observed for MPNs. Notable in the spectrum of **2**-C_{12}MPN are the olefinic protons of the maleimide moiety at 5.80 ppm and the $-CH_2-$ methylene protons α to the N at 3.40 ppm. The intense broad signal from ca. 1.1−2.0 ppm is mostly due to CH_2 resonances in the alkyl chains, and the smaller broad signal at 0.9−1.0 ppm is due to the terminal CH_3 group of the C_{12} ligand. The ratio of maleimide/C_{12} is estimated to be 1:2.2 on the particle, with slight variation from batch to batch depending on place-exchange conditions.[12]

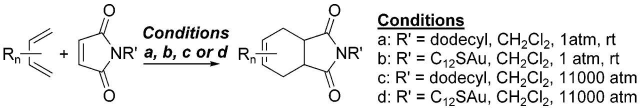
Scheme 1. Preparation of the Maleimide Modified MPN via the Retro-Diels−Alder Reaction of the Furan-Protected Maleimide



The prepared **2**-C_{12}MPN was then mixed with a 15 times molar excess of the appropriate diene (a−m) and dissolved in methylene chloride as the solvent. This mixture was then separated into two. One portion was purged with argon and left at ambient conditions (1 atm, 25 °C) and the other was placed in an argon purged Teflon tube and placed in a high-pressure reactor and subjected to pressures of ca. 162 Kpsi, which is equivalent to 1120 MPa, or 11000 atm. The minimum reaction time of the latter is ca. 10 min because of the time restrictions imposed by pressurization and depressurization.

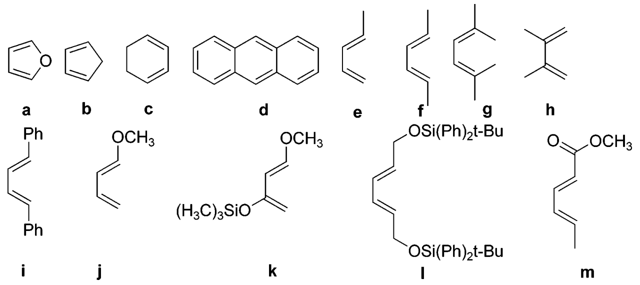
10.1021/ja070828m CCC: $37.00

Table 1. Times for Completion for the Diels−Alder Reactions of **2**-C$_{12}$MPN and *N*-dodecylmaleimide with Dienes a−m under Ambient and Hyperbaric Conditions[a]



diene	conditions a	conditions b	conditions c,d
a	70% in 7 d	7 d[b]	10 min
b	1 h (0 °C)	3 d (0 °C)	10 min
c	35 h	6 d	10 min
d	14 d	NR 21 d	10 min
e	3 d	70% in 7 d	10 min
f	3 d	60% in 7 d	10 min
g	NR	NR	NR 24 h
h	40 h	6 d	10 min
i	10% in 7 d	NR in 7 d	10 min
j	24 h	6 d	10 min
k	10 h	2 d	10 min
l	7 d	NR in 7 d	10 min
m	50% in 21 d	NR in 7 d	10 min

[a] Times indicate to reaction completion (or as indicated as determined by ^{1}H NMR spectroscopy; NR = no reaction. [b] Reaction run using 3000 times excess furan.



It should be noted that the reactions were not carried out at elevated temperature because high temperatures can lead to the decomposition of the MPN or stripping of ligands. For comparison, and to provide NMR spectra of the Diels−Alder adducts to compare to those obtained with the reactions carried out on the MPN, each diene was also mixed with *N*-dodecylmaleimide in CH$_2$Cl$_2$ and subjected to ambient and high-pressure conditions.

The progress of the reactions was monitored by ^{1}H NMR spectroscopy by the appearance of signals from the cycloadduct products and the disappearance of the signals due to the maleimide moiety. Absence of the latter was taken as completion of the reaction.[18] The results are summarized in Table 1. All dienes react much more readily with the model *N*-dodecylmaleimide (conditions a) than toward **2**-C$_{12}$MPN at ambient conditions (conditions b). In some cases there was no reaction toward **2**-C$_{12}$MPN after more than a week. Even the electron rich Danishefsky's diene (k) took 2 days to react with **2**-C$_{12}$MPN, whereas reaction with *N*-dodecylmaleimide was complete in about 10 h at 25 °C. The environment of the MPN must impose unique constraints on the orientation required for reaction. As expected, electron deficient or more sterically hindered dienes, such as d, i, l, m, reacted more sluggishly. Reactions of *N*-dodecylmaleimide with the same dienes at 11000 atm (conditions c) were completed in 10 min or less. Incredibly, the hyperbaric reactions of **2**-C$_{12}$MPN were also completed in 10 min or less (conditions d). Of the dienes investigated only 2,4-dimethyl-2,4-hexadiene (g) did not react at high pressures, presumably because of the high steric demands. ^{1}H NMR spectra of each of the **3**-C$_{12}$MPN adducts obtained are provided in the Supporting Information along with the spectral details of the corresponding reaction with the model dodecylmaleimide. The main and often exclusive stereoisomer was found to be the kinetic endo product; this is typical under high-pressure conditions. In the case of furan, the corresponding exo-endo isomers are easily identified and their ratio established. Noteworthy is that the extreme pressure conditions do not affect the core size of the MPN or otherwise alter its properties. The former was demonstrated in part by comparing TEM of the samples before and after being exposed to high-pressure conditions for over 24 h: the average core sizes did not change from the 2.5 ± 0.5 nm determined prior to exposure to hyperbaric conditions.

In summary, we demonstrate that hyperbaric pressure conditions can be used to facilitate interfacial Diels−Alder reactions in gold MPN environments that do not proceed efficiently at ambient pressure. Because the dramatic reaction acceleration using high pressure is unprecedented on metal nanoparticle surfaces the results suggest that hyperbaric conditions can be used to facilitate other reactions subject to hyperbaric acceleration (or retardation) in the MPN environment and be exploited to covalently link carbohydrates, proteins, nucleic acids, and other biomolecules using a Diels−Alder cycloaddition reaction. We are currently pursuing these ideas.

Acknowledgment. The authors thank the Natural Science and Engineering Research Council (NSERC) and The University of Western Ontario (ADF) for support of this work.

Supporting Information Available: General experimental details, details of the synthesis and characterization of **1**-C$_{12}$MPN, **2**-C$_{12}$MPN and dodecylmaleimide; ^{1}H NMR spectra of **3**-C$_{12}$MPN and characterization details of all Diels−Alder cycloadducts from dodecylmaleimide with the corresponding dienes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The extent of reaction was followed by ^{1}H NMR spectroscopy. Reactions were stopped at various times, the excess diene was removed by washing with 95% ethanol and acetonitrile and the NMR spectrum of the MPNs were measured. Reactions were deemed complete when the signals from the maleimide were absent.

JA070828M