

# Structure elucidation of nanoparticle-bound organic molecules by $^1\text{H}$ NMR

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The chemical nature of a nanoparticle surface determines its bioactivity and toxicity in vivo. Rational surface-chemistry modifications play a key role in modulating the toxicity of nanoparticles and applying nanotechnology to life sciences and medicine. However, there is a bottleneck in characterizing the organic molecules attached to the nanoparticle surface after such modifications.

This review summarizes recent developments in analysis of surface chemistry of nanomaterials using various proton nuclear magnetic resonance spectroscopy ( $^1\text{H}$  NMR) techniques. While these developments have had a substantial impact on nanoparticle-surface chemistry, more quantitative, flexible, and practical analytical techniques and strategies have still to be developed.

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## 1. Introduction

Medicines and diagnostic agents based on nanoparticles have the advantage of possessing many functions [1]. For example, to target disease cells specifically [2–4], such as cancer cells, targeting molecules are synthesized on the surface of nanoparticles. Such chemical modifications need to be carried out accurately and quantitatively with the assistance of analytical methods.

Furthermore, with the rapid development of nanotechnology and nanomedicine research, there is an ever-increasing concern about nanotoxicity [5]. Nanomaterials bind proteins [6], enter cells [7] or even the nucleus [8], and trigger cellular signaling pathways [9]. Cytotoxicity limits their applications in nanomedicine, nanodiagnostics, and consumer products.

However, the uniqueness of nanomaterials is their unusually large surface areas that control their biological activities. Chemistry modifications of their surface could regulate their activities, remove their toxic effects, and help them to perform the desired function. Altering surface coating of gold nanoparticles (GNPs) and

magnetic nanoparticles (MNPs) to enable only positive or negative charges has affected toxicity and cell permeability [10,11]. Parallel chemistry modifications [12] of MNPs and combinatorial chemistry modifications [13] of multi-walled carbon nanotubes (MWCNTs) have shown that careful design and modification of the chemistry of the surface of nanoparticles can control their biological activity and improve their biocompatibility.

With the development of microscopic technologies [e.g., transmission electron microscopy (TEM), scanning electron microscopy (SEM) and atomic force microscopy (AFM)], we have no shortage of methods to study the morphology of nanoparticles. However, chemical identification and quantification of small molecules linked to the surface of nanoparticles are very challenging because they are solid-phase samples and they are coated with only small amounts of small molecules. This has become a roadblock limiting our ability to modify nanomaterials chemically.

For this reason, some previous publications did not well characterize modified nanoparticles before doing biological

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testing. Biological experiments require precise identity or concentration information to obtain structure-activity and dose-response relationships. The lack of accurate identity or concentration information makes biological studies questionable or qualitative at most.

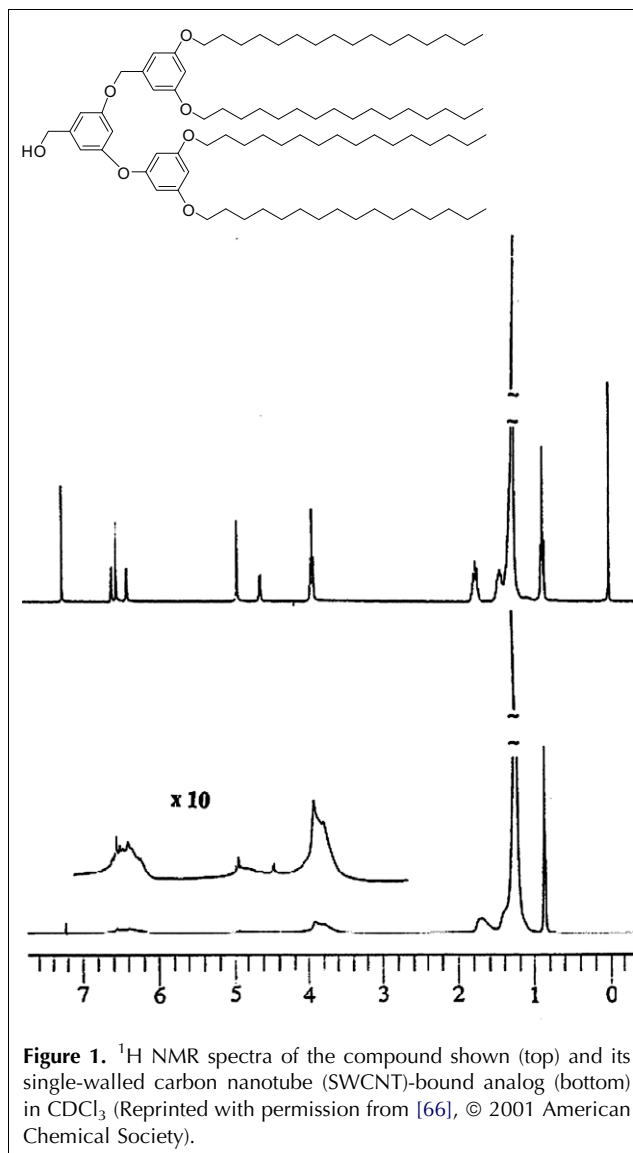
Nuclear magnetic resonance (NMR) spectroscopy is the gold standard for compound characterization in organic chemistry. There is also a long history in studying the nanoparticle-bound molecules using various NMR techniques [14–23]. In order to promote further development of suitable proton ( $^1\text{H}$ ) and other techniques to analyze nanoparticle chemistry, we reviewed recent progress in applying  $^1\text{H}$  NMR spectroscopy in nanoparticle research.

## 2. $^1\text{H}$ NMR of nanoparticle-bound molecules

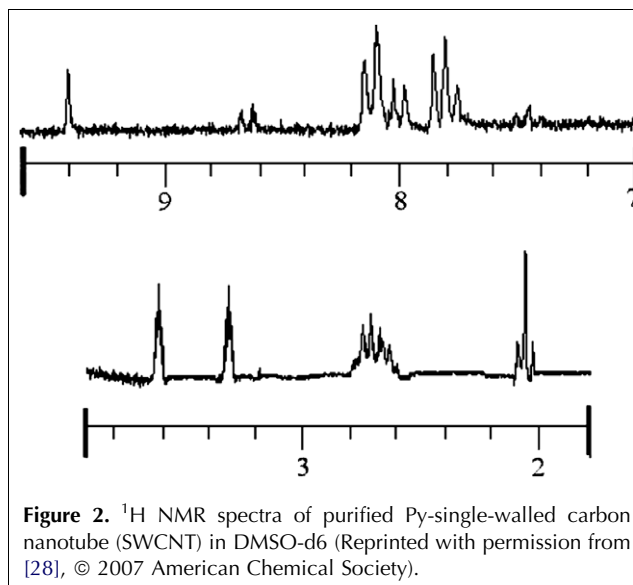
The power of solution NMR is often negated by the low solubility and the inhomogeneity of nanomaterials. When attached to a solid particle, the solution NMR signals of molecules bound to nanomaterials become broad [24–29] (Fig. 1).

Carbon nanotubes (CNTs) exhibit promising properties in both engineering and biomedical areas. Functionalization of single-walled CNTs (SWCNTs) has become a focus in many laboratories. Three different cycloaddition reactions were used to modify SWCNTs and formation of the products was monitored by  $^1\text{H}$  NMR [30]. A double functionalization of nanotubes with fluorescein isothiocyanate (FITC) and methotrexate (MTX), a widely used anti-cancer drug with low cellular uptake, was also reported [31]. In another study, carboxylic groups on SWCNTs (<200 nm length) were functionalized with 2, 6-diphenyl-4-(4-vinylbiphenyl) pyrylium (Py) [28], which is a strong electron-accepting photosensitizer moiety. Photoinduced electron transfer from SWCNTs to the Py caused an increase of positive charges on nanotube walls resulting in the deagglomeration of Py-SWCNTs through Coulombic repulsion. The Py-SWCNTs were characterized with high-resolution 400 MHz solution  $^1\text{H}$  NMR spectroscopy in DMSO. From the spectra (Fig. 2), the authors were able to observe the signals corresponding to the Py moiety in the aromatic region (7–9 ppm) and the mercaptopropyl-amine linkers in the aliphatic region (2–4 ppm).

Quantum dots (QDs) are nanoparticles with good solubility. It is possible to study the surface-bound molecules on these nanoparticles directly using  $^1\text{H}$  NMR.  $^1\text{H}$  NMR studies of thiophenol-coated cadmium sulfide (CdS) QDs were reported [32,33]. Using the shell model of Lippens and Lannoo [34] to predict the number of Cd atoms, the coverage of thiophenol molecules was calculated. The results showed that the coverage of thiophenol decreased from 26% to 5.6% as the size of the QDs were changed from 1.18 nm to 1.92 nm. When QDs



**Figure 1.**  $^1\text{H}$  NMR spectra of the compound shown (top) and its single-walled carbon nanotube (SWCNT)-bound analog (bottom) in  $\text{CDCl}_3$  (Reprinted with permission from [66], © 2001 American Chemical Society).



**Figure 2.**  $^1\text{H}$  NMR spectra of purified Py-single-walled carbon nanotube (SWCNT) in  $\text{DMSO-d}_6$  (Reprinted with permission from [28], © 2007 American Chemical Society).

became smaller, the resonances broadened, indicating that the rotation of the capping groups were more hindered in the smaller nanoparticles (1.2 nm) and the same groups became less hindered in the larger ones (2.0 nm). To distinguish free ligands from attached ligands, homonuclear decoupling experiments were used [35]. 2-ethylhexanoate-anion-stabilized CdS QDs were also synthesized [36], using  $^1\text{H}$  NMR for structural confirmation.

$^1\text{H}$  NMR was used to monitor ligand-exchange reactions on  $\text{SnO}_2$  nanoparticles [37].  $\text{SnO}_2$  nanoparticles were synthesized by exchanging the acetylacetonate (acacH)-stabilized  $\text{SnO}_2$  nanoparticles with the ligand 2-carboxyethanephosphonic acid (CEPA), as confirmed by NMR. When the oleic acid was used as trapping reagent for iron-oxide nanoparticles, the lack of vinyl and allyl proton resonances at 5.5 ppm and 2.0 ppm in the  $^1\text{H}$  NMR spectra was observed. It suggested that the double bond of oleic acid was reduced during nanoparticle synthesis [38]. Another ligand for the iron-oxide surface [39,40] was also designed and synthesized through copper(I)-catalyzed azide-alkyne cycloaddition. This reaction was named click chemistry and has been widely used in organic synthesis [41]. The structure was confirmed by solution  $^1\text{H}$  NMR through the characteristic peak at 8.0 ppm from the triazole proton.

In early studies of GNPs, the broad NMR peaks offered little information on the structure of bound molecules

[42]. However the absence of certain peaks could still indicate the complete removal of free ligands or phase-transfer catalysts.  $^1\text{H}$  NMR was used to monitor the synthesis of dodecanethiolated GNPs with different Au:ligand ratios [43]. The reaction of  $\text{Au}:\text{SC}_{12}\text{H}_{25}$  and iodosylbenzene was monitored using  $^1\text{H}$  NMR [44]. New sharp signals from dodecanal (Fig. 3, 9.55 ppm and 2.34 ppm for  $\text{CHO}$  and  $\text{CH}_2\text{CHO}$ , respectively) in solution revealed that the surface dodecyl groups were partially oxidized into dodecanal and eliminated from the cluster surface, thereby producing unprotected gold sites on the surface. At the same time, iodosylbenzene was reduced to iodobenzene (Fig. 3, 7.0–7.7 ppm). This conclusion was crucial for proposing a mechanism for the co-catalyst effect of gold nano clusters.

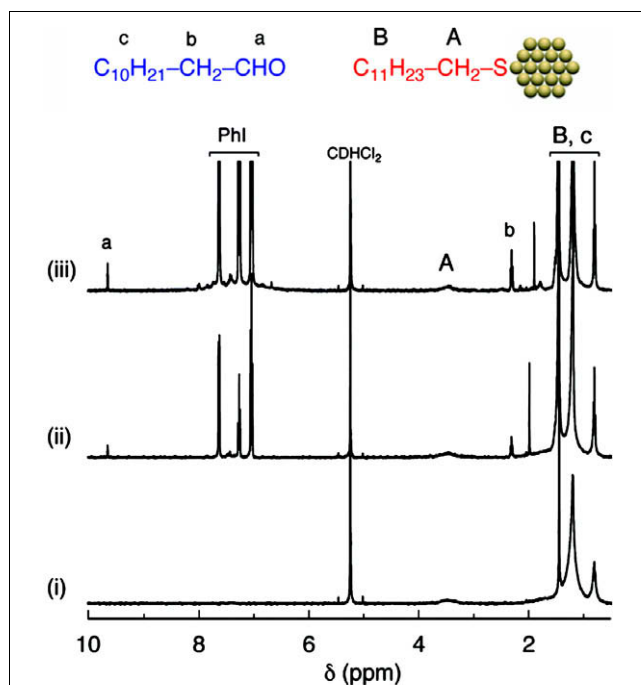
For the thiol-coated nanoparticles, an alternative method for structural characterization is to analyze the small molecules cleaved from the nanoparticles by oxidation with iodine [14]. However, the amount of nanoparticles needed depends on the loading of the small molecules on the surface. In one report, as much as 25 mg of GNPs was needed for decomposition reactions [45]. By indirectly analyzing the structure of the cleaved products, purity and structure information can be obtained [46,47]. Furthermore, this method can be used to monitor conversions during multi-step modifications. The drawback of this method is that it is time consuming and destructive.

These examples show that, although solution  $^1\text{H}$  NMR can provide some information, it is not very useful for a full structural elucidation. Several approaches were effective in overcoming this limitation as discussed in the following sections.

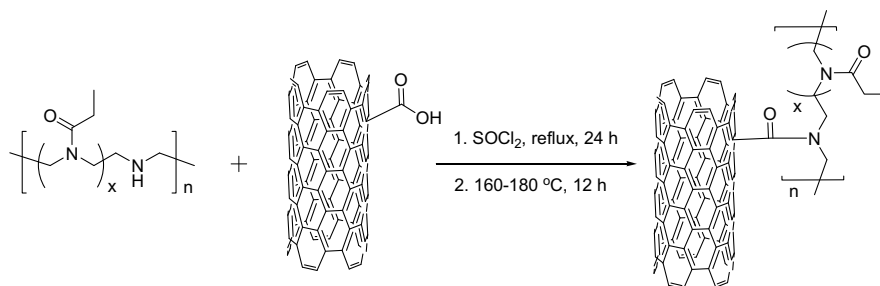
### 3. Enhancing $^1\text{H}$ NMR resolution with soluble, flexible linkers

A challenge for using nanoparticles in a biological system is their low solubility and poor bio-compatibility. One popular approach is to modify nanoparticles with hydrophilic polymers {e.g., cyclodextrin (CD) [48,49], carbohydrates [26,50], peptide [16,51] and polyethylene glycol (PEG) [52–54]}. The polymer-capped nanoparticles show enhanced solubility in aqueous solutions and reduced cytotoxicity. At the same time, the improved solubility makes it possible to use solution NMR for structural characterization.

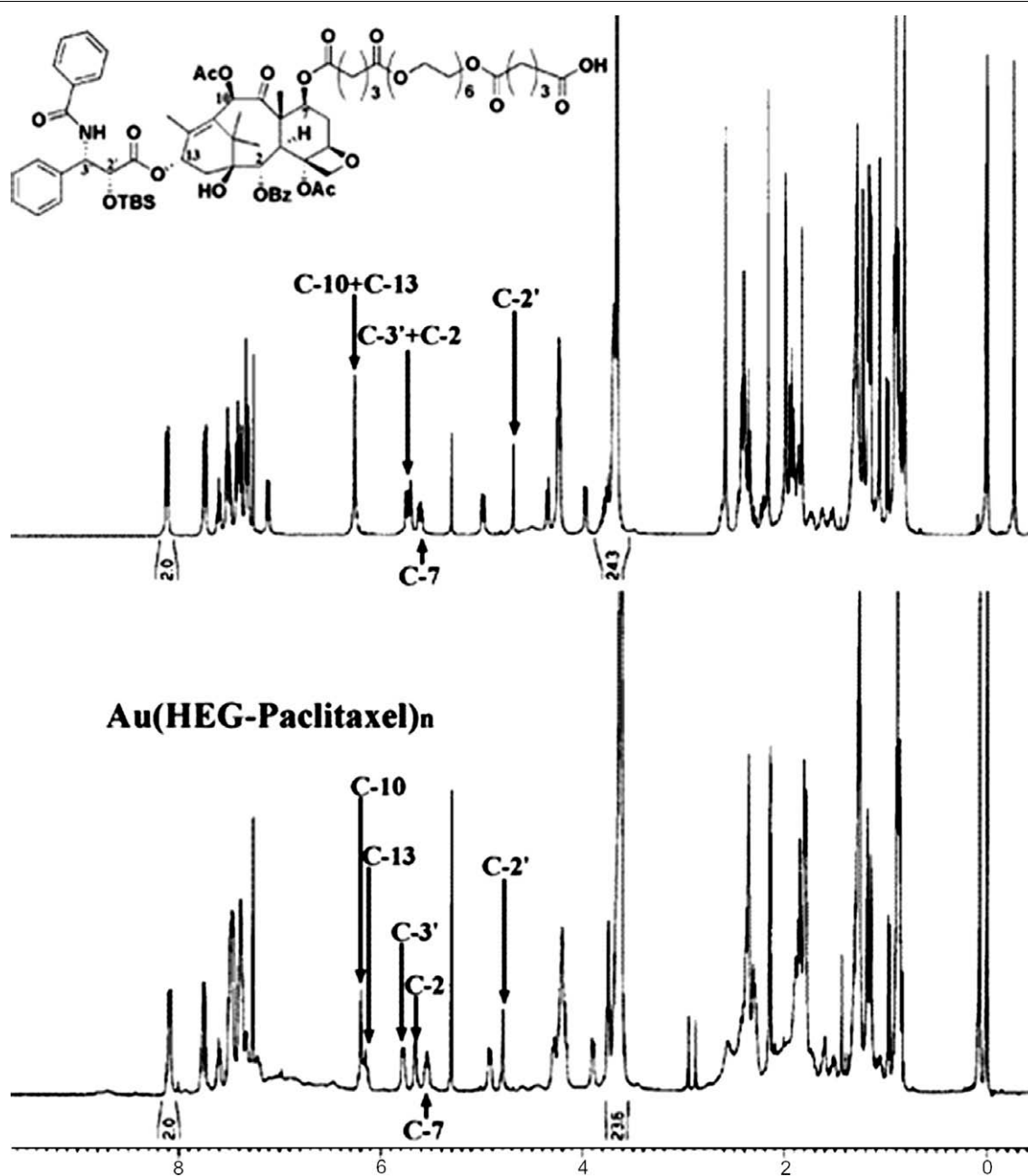
Poly(propionylethylenimine-co-ethylenimine) (PPEI-EI) was coupled to the surface of MWCNTs [24] by heating the carboxylated CNTs with PPEI-EI in the polymer melt (Scheme 1). The  $^1\text{H}$  NMR of the PPEI-EI polymer-functionalized MWCNTs was consistent with that of the parent PPEI-EI. A significant change was the absence of the signals at 2.8 ppm and 2.0 ppm due to the ethylenimine units in the functionalized MWCNTs. This indicated the amino moieties were responsible for the



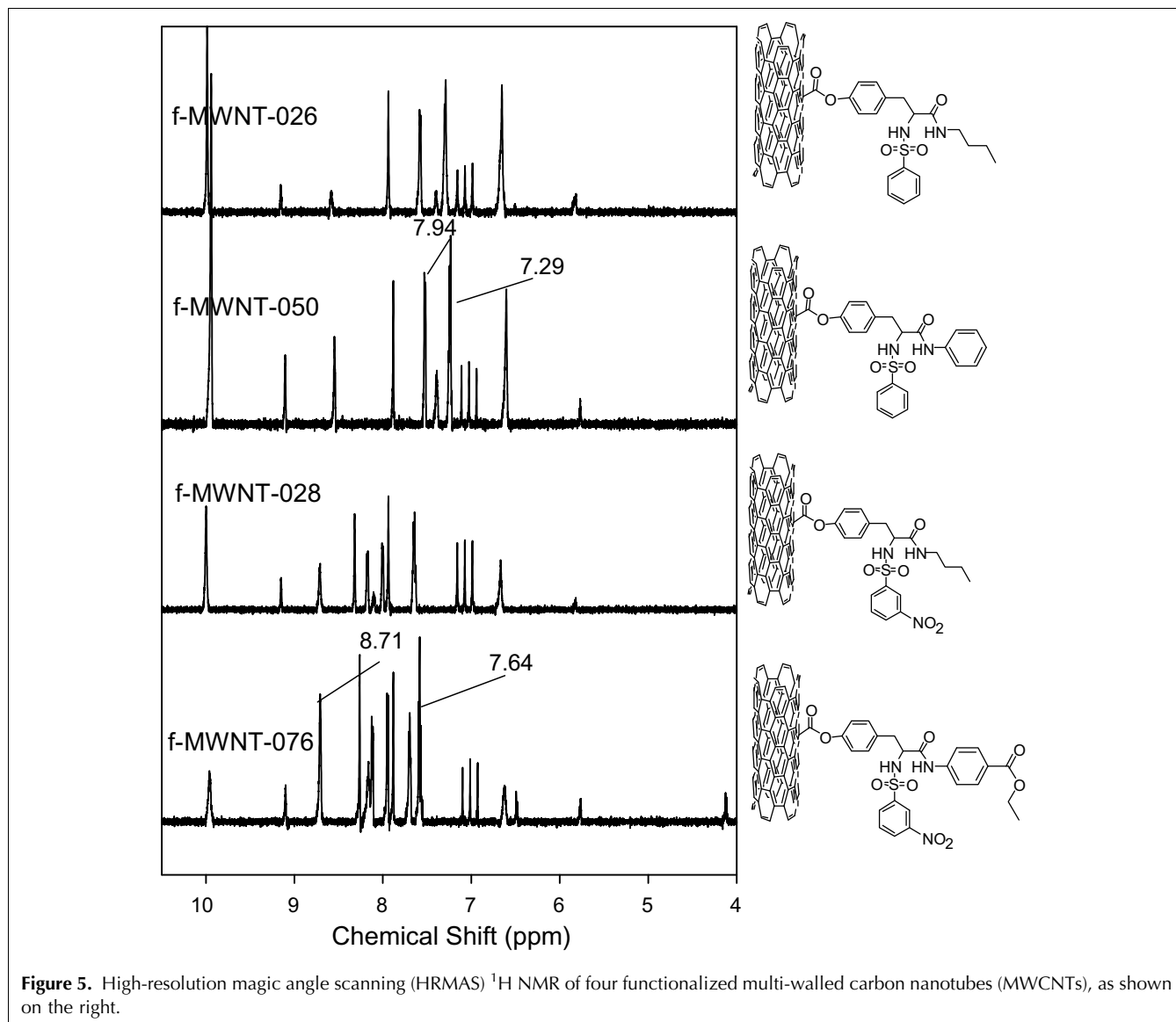
**Figure 3.**  $^1\text{H}$  NMR spectra of a gold nanoparticle-bound compound shown (0.067 mM): (i) before any reaction; (ii) after the reaction with 1000 equiv of iodosylbenzene for 1 h; and, (iii) after the same reaction for 5 h in  $\text{CD}_2\text{Cl}_2$  at  $25^\circ\text{C}$  (Reprinted with permission from [44], © 2007 American Chemical Society).



**Scheme 1.** Synthesis of poly(propionylethylenimine-co-ethylenimine) coupled to the walls of multi-walled carbon nanotubes.



**Figure 4.**  $^1\text{H}$  NMR spectra of paclitaxel analog (top) and the nanoparticle-bound analog (bottom) (Reprinted with permission from [57], © 2007 American Chemical Society).



functionalization with the carboxylic groups at the nanotube surface. Similarly, poly(2-diethylaminoethyl methacrylate) (PDEAEMA) was also used as a linker in the preparation of magnetic CNTs [55].

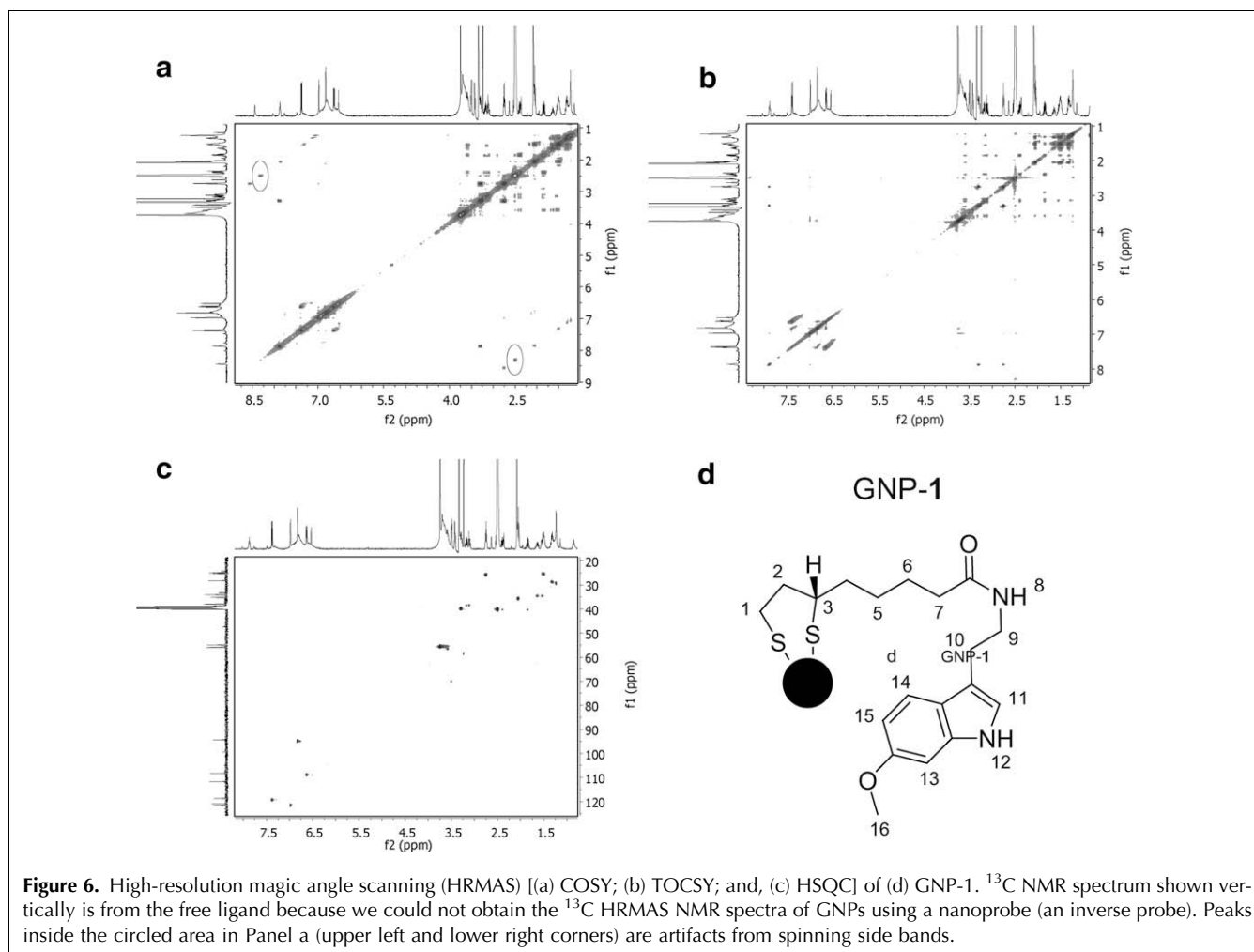
PEG, folic acid (FA), and PEG-FA were linked to MNPs [56] separately. By comparing the solution  $^1\text{H}$  NMR spectrum of PEG-FA with that of PEG-FA-NPs, authors were able to confirm the success of the surface-modification reaction because all characteristic peaks of the attached molecule were detected.

The enhancement of  $^1\text{H}$  NMR resolution was also demonstrated in the synthesis of anti-cancer drug paclitaxel (structure see Fig. 4) on GNPs through the inclusion of hexaethylene glycol (HEG) linker [57]. Authors found that nearly all resonances became exceedingly broad and unrecognizable if the paclitaxel molecule was directly coupled to the surface of GNPs without a HEG linker. Owing to the presence of the

highly flexible and relatively solvable HEG linker,  $^1\text{H}$  NMR quality was improved (Fig. 4). Comparing the spectra of free paclitaxel analogue (top) and the  $\text{Au}(\text{HEG-Paclitaxel})_n$  (bottom), signals between 7.2 ppm and 6.7 ppm were still very broad peaks due to the presence of the 4-mercaptophenol linker, which is closer to the surface of GNPs.

Coupling molecules to nanoparticles through a long, flexible, solvable linker can generally improve the spectra of nanomaterials. However, in reality, building such structures into the desired molecules is a synthetic challenge. Many reports still rely on regular solution NMR without inclusion of the polymer structure, as discussed in the previous section. Although such NMR analysis does not give the exact structural information, certain information can be obtained through the characteristic peaks that do not exist before the reaction.





#### 4. Structure characterization using $^1\text{H}$ MAS NMR and $^1\text{H}$ HRMAS NMR

From above survey, we found that routine NMR spectroscopy can monitor product formation, but is not an ideal method for full structure elucidation of organic molecules on the surface of nanomaterials.

It has long been recognized that magnetic-susceptibility-induced line broadenings in heterogeneous samples can be eliminated by spinning the sample at the magic angle ( $54.7^\circ$  from Z) [58]. The high-resolution magic-angle spinning (HRMAS) NMR technique was successfully used in 1990s in combinatorial chemistry applications [59–63].

We reported a nano-combinatorial library approach for chemical modification of MWCNTs and used  $^1\text{H}$  HRMAS NMR for structural characterization [13]. We found that different MWCNTs sharing the same benzenesulfonyl group had the same signals at 7.29–7.94 ppm (Fig. 5). MWCNTs sharing the same 3-nitro-benzenesulfonyl group had NMR peaks at 7.64–7.81 ppm. The existence of the nitro group reduced the electron

density and caused a downfield shift for aromatic protons.

Polito et al. [64] developed an efficient conversion for carbohydrate- and protein-derived MNPs via a surface diazo transfer/azide-alkyne click chemistry. Well-resolved  $^1\text{H}$  MAS NMR signals at around 8.0 ppm for all modified MNPs confirmed the presence of triazole protons.

Recently, we carried out full structural characterization of organic molecules attached to a GNP surface [65]. We optimized experimental conditions by selecting solvent, temperature, spin speed, and pulse sequence. Using one-dimensional and two-dimensional  $^1\text{H}$  NMR techniques, we were able to elucidate structures of all the attached molecules in our investigation.

Two-dimensional NMR spectra [e.g., correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY) and heteronuclear single quantum coherence (HSQC)] were recorded under optimized conditions (Fig. 6). These techniques were useful for complex structure characterization. Taking the COSY spectrum of GNP-1 as an example, it was used to assign the diagnostic

methene group (3) on the 5-member ring at 3.60 ppm. From this signal, the methylene group (2), which was split into two sets of peaks at 2.40 ppm and 1.85 ppm, was identified. The methylene group (1) next to the disulfide group was traced by the connectivity with these two peaks in the reverse direction at 3.18 ppm.

Two striking features were also discovered during our studies. Significant differences were found in detection sensitivity depending on the distance between the surface of GNPS and protons in the ligand molecule, with the loss of sensitivity for protons closer to the nanoparticles. Furthermore, NMR spectra of aromatic protons in ligands attached to GNPS seem to have a broad base compared with aliphatic ligands, indicating some degree of potential  $\pi - \pi$  stacking effects only for aromatic ligands.

## 5. Concluding remarks

The promise of using nanomaterials in therapy, medicine delivery, and diagnosis depends on their biocompatibility and targeting ability. The unusually large surface area of nanoparticles suggests that surface-chemistry modification would play a role in modulating their toxicity and biological specificity both in vitro and in vivo. It would not be surprising to see more focused and diverse chemistry modifications of nanomaterial surface in future research. However, reliable analysis of the identity and the quantity of surface-attached molecules remains a bottleneck. Various NMR techniques reviewed in this article have already played a key role in studying the relationship between surface chemistry and biological effects. However, full structural elucidation of attached molecules and quantification of their loading still require our continued dedication and efforts.

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