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Synthesis, Isomer Count, and Nuclear Spin Relaxation of H_2O@Open-C_{60} Nitroxide Derivatives

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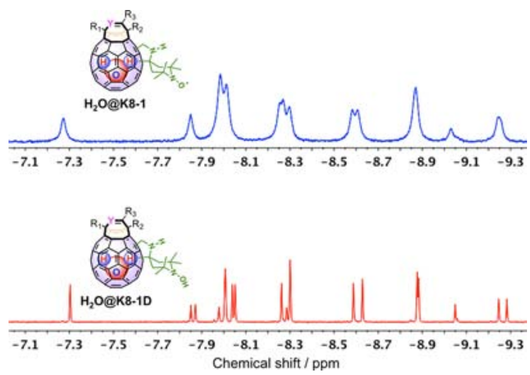
ABSTRACT



H_2O@C_{60} derivatives covalently linked to a nitroxide radical were synthesized. The ^{1}H NMR of the guest H_2O revealed the formation of many isomers with broad signals. Reduction to the diamagnetic hydroxylamines sharpened the ^{1}H NMR signals considerably and allowed for an "isomer count" based on the number of observed distinct signals. For H_2O@K-8, 17 positional isomeric nitroxides are predicted, not including additional numbers of regioisomers; indeed, 17 signals are observed in the ^{1}H NMR spectrum.

Fullerene C_{60} derivatives covalently linked to a nitroxide radical have been synthesized and extensively studied by time-resolved electron paramagnetic resonance spectroscopy (TREPR) in order to probe the interaction between the triplet state of C_{60} and the nitroxide radical.[1−3] Two common synthetic methods have been used to prepare the C_{60} nitroxide derivatives: the Prato (fulleropyrrolidines)[4,5] and the Bingel (methanofullerenes)[6] reactions.

Due to the availability[7] of the endohedral H_2@C_{60} in our lab, we have extensively investigated the interaction between the endo-H_2 and the outside environment via nitroxide radicals covalently attached to the H_2@C_{60} cage.[8] We found that the intramolecular relaxation effect on the endo-H_2 from a nitroxide radical attached with a short

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(1) Arena, F.; Bullo, F.; Conti, F.; Corvaja, C.; Maggini, M.; Prato, M.; Scorrano, G. *J. Am. Chem. Soc.* **1997**, *119*, 789–795.
(2) Corvaja, C.; Maggini, M.; Prato, M.; Scorrano, G.; Venzin, M. *J. Am. Chem. Soc.* **1995**, *117*, 8857–8858.
(3) Sartori, E.; Toffoletti, A.; Corvaja, C.; Garlaschelli, L. *J. Phys. Chem. A* **2001**, *105*, 10776–10780.
(4) Corvaja, C.; Conti, F.; Franco, L.; Maggini, M. *C. R. Chimie* **2006**, *9*, 909–915.
(5) Prato, M.; Maggini, M. *Acc. Chem. Res.* **1998**, *31*, 519–526.
(6) Bingel, C. *Chem. Ber.* **1993**, *126*, 1957–1959.
(7) Komatsu, K.; Murata, M.; Murata, Y. *Science* **2005**, *307*, 238–240.
(8) Li, Y.; Lei, X.; Lawler, R. G.; Murata, Y.; Komatsu, K.; Turro, N. J. *J. Phys. Chem. Lett.* **2010**, *1*, 2135–2138.
(9) Sartori, E.; Ruzzi, M.; Turro, N. J.; Komatsu, K.; Murata, Y.; Lawler, R. G.; Buchachenko, A. L. *J. Am. Chem. Soc.* **2008**, *130*, 2221–2225.

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spacer is much stronger than could be achieved with any realistic concentration of an external relaxant.[9]

Recently, a water molecule encapsulated in a C_{60} cage has been successfully synthesized by the molecular surgery method.[10] The availability of substantial amounts of $H_2O@C_{60}$ enables us to explore the interactions between the endo-H_2O and the outside environment. We have reported[11] the nuclear spin relaxation (T_1) of $H_2O@C_{60}$ and two of its nitroxide derivatives. A comparison with the corresponding $H_2@C_{60}$ nitroxide derivatives[8] indicates that both systems produce T_1 enhancements that are consistent with similar through-space interaction between the internal nuclear spins and the external electron spin. We have also compared[11] the nuclear spin relaxation of H_2 and H_2O encapsulated in C_{60} produced by an external relaxant,[9] such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), and find similar effects for both endo molecules.

Open-form C_{60} derivatives (see Figure 1) were available to us as intermediates in the synthesis[7,10] of $H_2@C_{60}$ and $H_2O@C_{60}$. An interesting issue is a comparison of the effectiveness of nitroxides attached to the fullerene cage in enhancing the T_1 relaxation of guest H_2 and H_2O molecules. In other words, how does a hole in the C_{60} cage influence the magnetic communication between the internal endomolecule and the external nitroxide radical. However, because of the low symmetry of the open forms, a large number of monosubstituted nitroxides might be formed. This brings up an interesting issue of how many mononitroxides of the open cages are possible and experimentally how many are formed, and how to identify the number of isomers produced in the synthesis.

^{3}He NMR spectroscopy[12] has been employed to provide structural information on complex mixtures derived from bis additions to $^3He@C_{60}$. Well separated signals were observed over a spectral range of 2 ppm.[12] The excellent separation of the signals shows that the magnetic field experienced by the ring currents of the π-system is exquisitely sensitive to the patterns of attachment of added groups to the C_{60} surface.[12] The authors point out that ^{3}He NMR is an excellent and sensitive tool for determining the ratio as well and the identity of fullerene adducts.

By analogy with the ^{3}He measurements, we recently reported[13] that bisadduct isomers of $H_2@C_{60}$ derivatives can be differentiated by ^{1}H NMR spectroscopy of the endo-H_2. The high sensitivity and short T_1 of ^{1}H NMR spectroscopy make this a very promising method in identifying $H_2@C_{60}$ derivative isomers.

We synthesized the open-form endohedral C_{60} nitroxide derivatives following the same procedures used for the preparation[8,11] of $H_2@1$ and $H_2O@1$ (Figure 1). The reaction with the open-form C_{60} yielded a mixture of C_{60} nitroxide derivative isomers. In the case of $H_2O@K8$ (Figure 1), a total of 17 isomers, corresponding to 17 distinct double bonds, are possible because the molecule has a symmetry plane across the bridge of the orifice. Additional regioisomers can be formed depending on the orientation of the attached nitroxide group.[14] [A Schlegel diagram is included in the Supporting Information (Figure S1) showing the location of the double bonds and also the rings and bridges in the open forms].

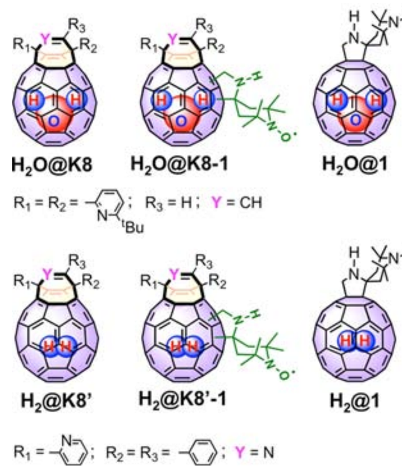

Figure 1. Structures used in this study.

The reaction mixture was purified by column chromatography (silica gel; eluent: toluene/ethyl acetate 19:1, v/v). The starting material was recovered as the first fraction followed by the nitroxide isomers as the second fraction. Mass spectroscopy in FAB+ mode (Figures S2 and S3, Supporting Information) confirms that only monoadduct isomers were included in the second fraction.

The ^{1}H NMR spectrum for the region from -7 to -9 ppm of the mixture of nitroxide isomers (endo-H_2O region) is shown in Figure 2a. The chemical shifts of the various isomers are distributed over *ca.* 2 ppm in a region about 2 ppm upfield from endo-H_2O in the parent open fullerene, which is similar in extent and position to what was observed with our previously reported $H_2@C_{60}$ nitroxide bisadducts[13] and the NMR[12] of endo ^{3}He in analogous bisadducts. However, because of the broadening effect from the attached nitroxide radical, some of the individual signals overlap and distinct isomers cannot be detected. The broad signals are caused by the paramagnetic influence of the attached nitroxide. The broadness is conveniently removed by reduction[15] of the nitroxides to the corresponding diamagnetic hydroxylamines using hydrazobenzene.

The ^{1}H NMR spectrum of the mixture of reduced isomers is shown in Figure 2b. Once the nitroxide radical was completely reduced (confirmed by disappearance of

(10) Kurotobi, K.; Murata, Y. *Science* **2011**, *333*, 613–616.
(11) Li, Y.; Chen, J. Y.-C.; Lei, X.; Lawler, R. G.; Murata, Y.; Komatsu, K.; Turro, N. J. *J. Phys. Chem. Lett.* **2012**, *3*, 1165–1168.
(12) Cross, J. R.; Jimenez-Vazquez, H. A.; Lu, Q.; Sanuders, M.; Schuster, D. I.; Wilson, S. R.; Zhao, H. *J. Am. Chem. Soc.* **1996**, *118*, 11454–11459.
(13) Li, Y.; Lei, X.; Lawler, R. G.; Murata, Y.; Komatsu, K.; Turro, N. J.; Turro *Chem. Commun.* **2011**, *47*, 2282–2284.
(14) Ohba, Y.; Nishimura, M.; Mizuochi, N.; Yamauchi, S. *Appl. Magn. Reson.* **2004**, *26*, 117–134.
(15) Li, Y.; Lei, X.; Li, X.; Lawler, R. G.; Murata, Y.; Komatsu, K.; Turro, N. J. *Chem. Commun.* **2011**, *47*, 12527–12529.

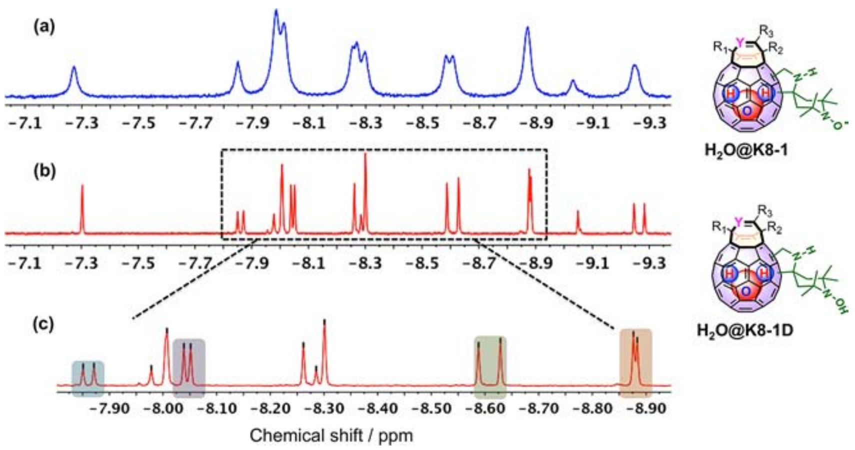

Figure 2. [1]H NMR of endo-H_2O in toluene-d_8 solutions. (a) A mixture of isomers of H_2O@K8-1; (b) a mixture of isomers of H_2O@K8-1D after reduction of H_2O@K8-1 by hydrazobenzene (~10 equiv); (c) expanded spectrum. Each peak is labeled by a black dot. The four sets of doublets with highlights are probably from the regioisomers of each positional isomer.

the EPR signal from the reacted sample), the NMR peaks of the endo-H_2O become narrower and the overlap between distinct signals is diminished. The total peaks found for the endo-H_2O are 17. While it is possible that each peak represents a reaction at one of the 17 double bonds in the starting material, it seems more likely that some of the peaks correspond to pairs of regioisomers arising from the two different orientations[14] of the nitroxide ring relative to the opening in the fullerene. Further separation of each isomer is needed in order to confirm whether the [1]H NMR spectrum of the endo-H_2O is selective enough to differentiate the regioisomers that are due to the variable orientations of the attached nitroxide group. This work is under investigation.

For comparison, we also synthesized the lower symmetry H_2@K8′ nitroxide derivative isomers (Figure 1) using the intermediate commonly used for the preparation of $H_2@C_{60}$. The [1]H NMR spectrum of the endo-H_2 is shown in Figure 3a. Up to 30 isomers can be formed for H_2@K8′ due to the 30 distinct double bonds arising from the lack of any symmetry element in the molecule. After reducing with hydrazobenzene, 27 peaks were detected in the [1]H NMR spectrum of the endo-H_2 in the reduced products (Figure 3b).

Nuclear spin relaxation (T_1) of some of the isomeric adducts exhibiting the least overlapped peaks of H_2O@-K8-1 and H_2@K8′-1 in toluene-d_8 solution at 300 K was measured at 500 MHz using the standard inversion–recovery method (Tables S1–S4, Supporting Information). The range of values of T_1 is 35–40 ms for isomers of H_2O@K8-1 and 27–31 ms for isomers of H_2@K8′-1, respectively (Table 1). In comparison with the corresponding C_{60} nitroxides[11] (T_1 of H_2O@1: 59 ms; T_1 of H_2@1: 51 ms) under the same conditions, both values of T_1 of both the open-C_{60} nitroxides are decreased, consistent with the somewhat longer rotational correlation time for the larger fullerene cage.

The longer T_1 values for the diamagnetic species (H_2O@K8-1D and H_2@K8′-1D) are similar to those of the corresponding open forms (Table 1), consistent with the previous conclusion that the relaxation of both endo molecules is dominated by the rotational motion of the molecule itself and is insensitive to the slower motion of the cage.[11] Careful comparison of the chemical shifts of the best-resolved NMR peaks for the nitroxide with the correpsonding peaks in the hydroxylamine (Tables S1–S4, Supporting Information) reveals an upfield shift of 10–15 Hz for the latter for both endo H_2O and H_2, slightly smaller than the shift of 20 Hz observed previously for the $H_2@C_{60}$ derivatives.[13]

Table 1. T_1 Values of Endohedral Fullerene Derivatives and Open Forms

compd	T_1/ms[a]	compd	T_1/ms[a]
H_2O@1	59	**H_2@1**	51
H_2O@K8–1	35–40	**H_2@K8′-1**	27–31
H_2O@K8–1D	1800–2700	**H_2@K8′-1D**	138–160
H_2O@K8	2500	**H_2@K8′**	137

[a] 500 MHz, room temperature in toluene-d_8.

Further inspection of some of the measurable T_1 values of H_2O@K8-1D indicates four sets of doublet features for which the T_1's of each of the two components are nearly the same (Table 2 and Figure 2c highlighted). We speculate that these doublets could be due to the two regioisomers of each positional isomer. It might be expected that, compared to the positional isomers, the effect on the reorientational motion of the fullerene, and resulting T_1 values, produced by changing the orientation of the attached nitroxide group should be reduced.

In summary, for the first time, we have synthesized open-form $H_2O@C_{60}$ and $H_2@C_{60}$ mononitroxide derivatives

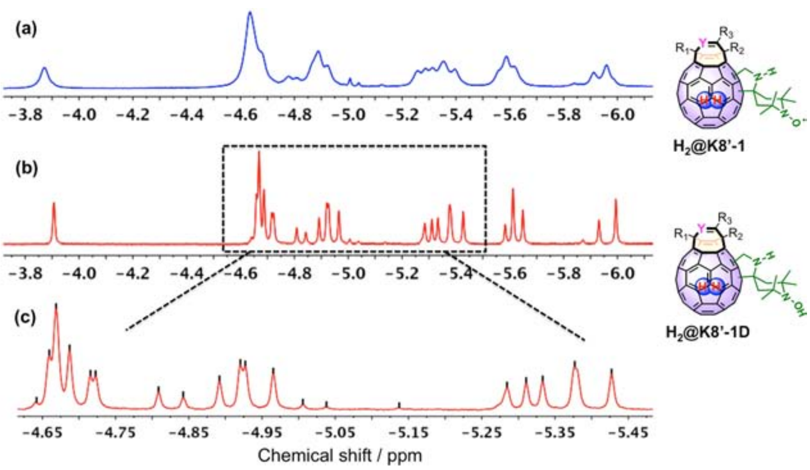

Figure 3. ^{1}H NMR of endo-H_2 in toluene-d_8 solutions. (a) A mixture of isomers of H_2@K8′-1; (b) a mixture of isomers of H_2@K8′-1D after reduction of H_2@K8′-1 by hydrazobenzene (10 equiv); (c) expanded spectrum. Each peak is labeled by a black dot.

Table 2. Chemical Shifts and T_1 Values of H_2O@K8-1D Isomers

entry	chemical shift/ppm	T_1/s[a]
1	−7.303	1.81
2	−7.841	1.93
3	−7.861	1.91
4	−8.007	2.58
5	−8.038	2.01
6	−8.050	2.05
7	−8.261	2.23
8	−8.301	2.35
9	−8.589	2.18
10	−8.629	2.19
11	−8.878	2.39
12	−8.885	2.32
13	−9.248	2.34
14	−9.282	2.57

[a] 500 MHz, room temperature in toluene-d_8.

and an array of isomers are detected by employing the ^{1}H NMR spectrum of the corresponding endo-H_2O/H_2 moieties. Proton relaxation times for the endo H_2O and H_2 are nearly the same for all isomers and differ from the values in the corresponding C_{60} nitroxides in the direction expected on the basis of the size of the cage. The study demonstrates that the ^{1}H NMR spectrum of the endohedral molecule (H_2 or H_2O) is an excellent probe in detecting newly synthesized endohedral C_{60} derivatives. We note that the ^{1}H signals in H_2@C_{60} or H_2O@C_{60} fullerenes appear to have an exquisite sensitivity to structure and show signal sharpness similar to that exhibited by the ^{3}He signals[12] in isomeric endofullerene bis-adducts. Most importantly, the high field chemical shift region of the ^{1}H NMR spectrum characteristic of both endo molecular probes is free of background signals from solvent or nonfullerene impurities.

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Supporting Information Available. Mass spectra, T_1 values of some of isomeric adducts of H_2O@K8-1, H_2@K8′-1, and H_2@K8′-1D, and a Schlegel diagram. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.