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# Paramagnet Enhanced Nuclear Spin Relaxation in $H_2O$@Open-$C_{60}$ and $H_2$@Open-$C_{60}$

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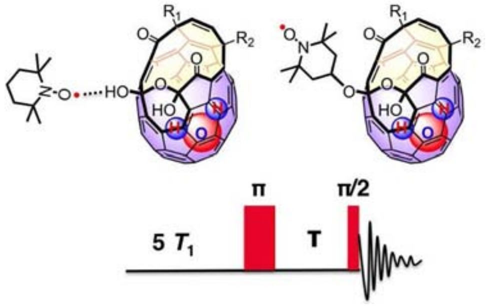
## ABSTRACT



**Relaxation rates of *endo*-$H_2O$ in $H_2O$@Open-$C_{60}$ in the presence of a nitroxide radical and of their nitroxide derivatives have been measured and are compared with effects for *endo*-$H_2$ in similar cages. $T_1$ relaxation enhancement of the *endo*-$H_2O$ and $H_2$ induced by either intra- or intermolecular interaction is relatively insensitive to the presence of a cage opening. Enhancement of intermolecular relaxation is observed, however, when the cage opening has an OH group.**

In a recent paper,[1] we reported the synthesis and nuclear spin relaxation of $H_2O$ in a $H_2O$@Open-$C_{60}$ paramagnetic nitroxide derivative with an eight-membered ring opening in the $C_{60}$ cage. Such enhancement of relaxation by paramagnetic catalysts plays an important role in developing methods for enriching spin isomers of small molecules encapsulated in fullerene cages for possible applications in magnetic resonance imaging or other practical purposes.[2,3] Due to the availability of multiple double bonds on the $C_{60}$ cage and the unsymmetrical features of the product molecule, a variety of isomers were obtained and differentiated by proton NMR spectroscopy of the *endo*-$H_2O$. We measured and briefly discussed the relaxation times ($T_1$) of some of the $H_2O$@Open-$C_{60}$ nitroxide isomers. The results were compared with those of structurally similar nitroxide isomers of a $H_2$@Open-$C_{60}$ compound.[1] Similar methodology was employed to attach a nitroxide to the parent $H_2O$@$C_{60}$ cage.[4] This made it possible to compare the relaxation properties of $H_2O$ and $H_2$ inside the same cage with and without an attached paramagnet.[4] The relative sensitivities of the two *endo* molecules to enhancement of the relaxation rate, $1/T_1$, i.e. relaxivity, $R_1$ ($M^{-1}s^{-1}$), by bimolecular encounters with a nitroxide paramagnet were also determined.[4]

We present here an extension of these measurements to include the relaxivity of two Open-$C_{60}$ *endo* fullerenes containing $H_2O$ or $H_2$ induced by a nitroxide. We also

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report the paramagnetic contribution to $T_1$ for a newly synthesized $H_2O$@Open-$C_{60}$ nitroxide derivative, $H_2O$@K13-1, containing a 13-membered ring opening in the cage (Figure 1). For the most part, opening the fullerene cage produces only modest changes in the effectiveness of the paramagnetic relaxation enhancement of *endo*-$H_2O$ and -$H_2$. It is found, however, that relaxation by an external nitroxide is strikingly increased by the presence of an OH group on the periphery of the cage opening. This is consistent with an increase in the contact time beween the fullerene and paramagnet due to hydrogen bonding.

In principle, there are four ways to enhance the $T_1$ relaxation of *endo*-$H_2O$ or *endo*-$H_2$ in a fullerene by a paramagnetic species such as a nitroxide radical:

1) As we already reported,[1] a nitroxide radical can be covalently attached to the open-$C_{60}$ cage. The $T_1$ relaxation enhancement is *via* the intramolecular dipole−dipole interaction in this case.
2) Instead of being part of a framework mounted on the $C_{60}$ cage, the nitroxide radical can be covalently attached to a functional group on the orifice of the open-cage $C_{60}$, a type of derivatization that is not available with unfunctionalized fullerenes. In this case, the $T_1$ relaxation enhancement of *endo*-$H_2O$ is also caused by the intramolecular dipolar interaction with the nitroxide radical.
3) Without synthesizing a new $H_2O$@Open-$C_{60}$ nitroxide derivative, as in cases 1 and 2, it is possible to simply add nitroxide radicals (such as TEMPO) to the solution of fullerene.[5,6] In this case, bimolecular, i.e. intermolecular, relaxation occurs between the *endo* nuclei and the unpaired electron during a collision between the partners.
4) Based on case 3, $T_1$ relaxation should be further enhanced if the added nitroxide radical can form a hydrogen bond or another noncovalent interaction with a functional group on the orifice of the open fullerene. The relaxation then would correspond to an inner-sphere mechanism.

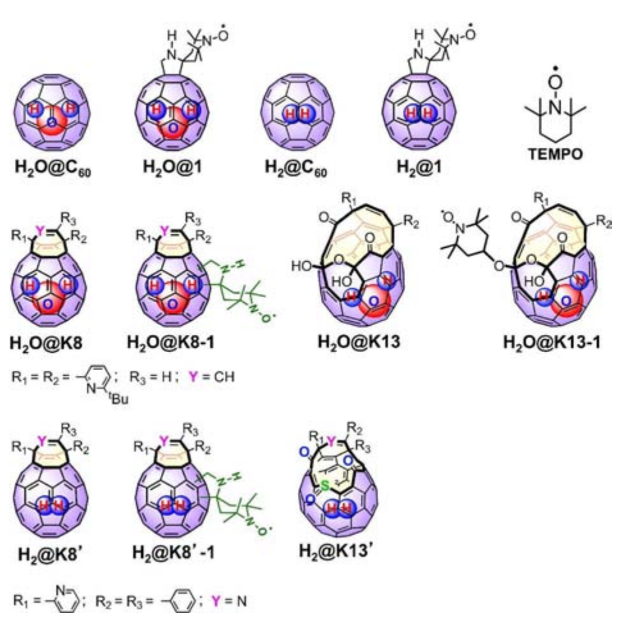

**Figure 1.** Structures used in this study.

For case 1, we have already synthesized the nitroxide derivatives and measured the paramagnetic contribution to $T_1$.[1,4,7] Case 3 is a routine experiment and can be done conveniently, subject to sufficient solubility of the paramagnetic relaxant and fullerene. For case 2, one has to modify the orifice of the open-$C_{60}$ cage to make it available for further chemical functionalization. Fortunately, one of the open-$C_{60}$ compounds, $H_2O$@K13 (Figure 1) that is an intermediate for synthesizing $H_2O$@$C_{60}$ by the molecular surgery methodology,[8,9] has two hydroxyl groups on the orifice that provide a possibility for covalently attaching a nitroxide radical. Finally, it should be noted that the hydroxyl group on the orifice also provides the possibility for a hydrogen-bonding interaction with the nitroxide radical (case 4, Figure 2).

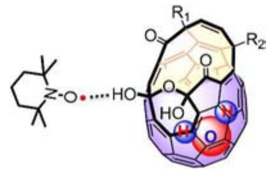

**Figure 2.** Proposed structure of $H_2O$@K13 hydrogen bonded with TEMPO.

We report here $T_1$ relaxation enhancements of *endo*-$H_2O$ in a $H_2O$@Open-$C_{60}$ in the presence of TEMPO and in $H_2O$@Open-$C_{60}$ nitroxide derivatives and compare the results with those for some analogous *endo*-$H_2$ compounds. The structures of the relevant molecules are shown in Figure 1. The $T_1$ and relaxivity measurements are summarized in Tables 1 and 2, respectively.

The results may be summarized as follows:

**Case 1. Intramolecular relaxation by nitroxide mounted on the cage wall.** The distance, $d$, between the unpaired electron on the attached nitroxide auxiliary and the center of the fullerene cage is expected to be constant through the series of four *endo* fullerenes $H_2O$@1, $H_2O$@K8-1, and their $H_2$ analogues. The value of $d$ estimated from molecular modeling is 8.9 Å.[7] It would therefore be expected that the paramagnetic contribution to

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**Table 1.** Paramagnetic Contribution to Relaxation, $1/T_{1,p}$ ($s^{-1}$), by an Attached Nitroxide for $H_2O@C_{60}$, $H_2@C_{60}$, and Derivatives (Figure 1)[a]

| compds | $1/T_{1,p}$ ($s^{-1}$) | compds | $1/T_{1,p}$ ($s^{-1}$) |
|---|---|---|---|
| **$H_2O$@1** | $16^b$ | **$H_2$@1** | $13^b$ |
| **$H_2O$@K8-1** | $27 \pm 1^c$ | **$H_2$@K8′-1** | $29 \pm 2^c$ |
| **$H_2O$@K13-1** | 15 | – | – |

[a] Unless otherwise indicated measurements in toluene-$d_8$, 300 K. [b] Reference 4. [c] Reference 1; average for two isomers with well-resolved NMR peaks.

**Table 2.** Relaxivity, $R_1$ (TEMPO, $M^{-1}$ $s^{-1}$), for $H_2O@C_{60}$, $H_2@C_{60}$, and Derivatives (Figure 1)[a]

| compds | $R_1$ ($M^{-1}$ $s^{-1}$) | compds | $R_1$ ($M^{-1}$ $s^{-1}$) |
|---|---|---|---|
| **$H_2O@C_{60}$** | $43 \pm 3^b$ | **$H_2@C_{60}$** | $129 \pm 18^c$ |
| **$H_2O$@K8** | $41 \pm 4$ | **$H_2$@K8′** | $50 \pm 5^c$ |
| **$H_2O$@K13** | $248 \pm 4$ | **$H_2$@K13′** | $48 \pm 2^c$ |

[a] Unless otherwise indicated measurements in toluene-$d_8$, 300 K. [b] Reference 4. [c] 1,2-Dichlorobenzene-$d_4$, 300 K.

relaxation, $T_{1,p}$, would be the same for all four compounds, subject to the details of rotation of the small *endo* molecules that might affect the average distance of the $H_2O$ or $H_2$ protons from the center of the cage. Here $1/T_{1,p}$ is the relaxation rate caused by the paramagnetic species and calculated based on[5] the following equation: $1/T_{1,p} = (1/T_{1,obs} - 1/T_{1,d})$ where $T_{1,obs}$ is the observed relaxation time, and $T_{1,d}$ is the relaxation time in the absence of the paramagnetic center, i.e., the hydroxylamine derivatives (the reduction product of the nitroxide derivative[4]) in the current system. Furthermore, the relaxation rate coefficient, $1/T_{1,p}$, is expected[7] to vary as the inverse sixth power of the distance and is therefore quite sensitive to small changes in $d$. The data in Table 1 show, indeed, that the values of $1/T_{1,p}$ vary only 2-fold through the series, and less than that between $H_2O$ and $H_2$ in the same type of cage.[1,4] Interestingly, the cage opening seems to enhance somewhat the effect of a paramagnetic auxiliary. This may reflect small changes in cage geometry or dynamics that reduce the effective average distance between the paramagnet and the interior protons. The longer rotational correlation time for the larger, "rougher" open fullerene cage would also be expected to increase the effectiveness of the intramolecular dipolar relaxation mechanism.[7]

**Case 2. Intramolecular relaxation by nitroxide attached to functional group.** Since there are two hydroxyl groups on the orifice of $H_2O$@K-13, it is possible to covalently attach a nitroxide radical derivative to the orifice. Therefore, the coupling reaction between 4-hydroxyl TEMPO and $H_2O$@K13 was attempted. After several trials, we successfully synthesized $H_2O$@K13-1 (see Supporting Information for synthetic details). Due to steric hindrance, only one of the two hydroxyl groups was coupled with 4-hydroxyl-TEMPO (The assignment of the functionalized OH group shown in Figure 1 is arbitrary and only illustrative.). The proton NMR spectrum of *endo*-$H_2O$ in $H_2O$@K13-1 shifts further to high field (−9.95 ppm) relative to $H_2O$@K13 (−9.93 ppm) (Figure 3). The presence of the nitroxide radical broadens the NMR peak. The value of $1/T_{1,p}$ for the paramagnetic compound $H_2O$@K13-1 is nearly the same as that for the closed cage compound $H_2O$@1 and its $H_2$ analogue and about half of that for the series of derivatives $H_2O$@K8-1. The $H_2$ analogue of $H_2O$@K13-1 has not yet been prepared since it will require moving synthetically beyond the intermediates prepared during the standard molecular surgery process.[7,8] Further study of the relatively small difference in $1/T_{1,p}$ between $H_2O$@K13-1 and the other compounds would require estimating an effective value of $d$ that arises from averaging over the possible conformations of the attached nitroxide ring. This complication is avoided with the more rigid attachment framework of the other nitroxides.

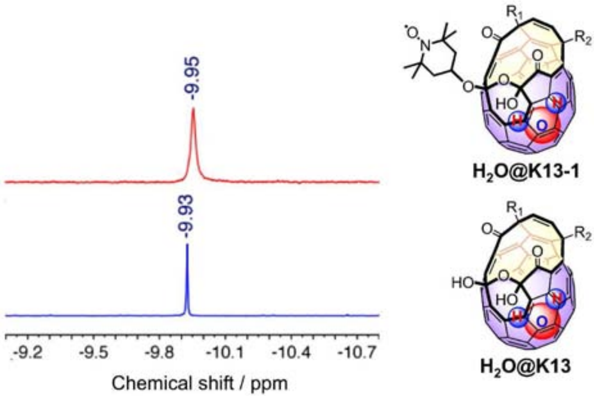

**Figure 3.** $^1H$ NMR spectra of *endo*-$H_2O$ in **$H_2O$@K13−1** and **$H_2O$@K13** in $CDCl_3$.

**Case 3. Relaxivity induced by intermolecular interactions with nitroxide.** The $T_1$ relaxation times of $H_2O$ in $H_2O$@K8 and $H_2O$@K13 in the presence of TEMPO in toluene-$d_8$ solutions were measured using the standard inversion−recovery method.[6] The resulting relaxation rates ($1/T_1$) versus concentration of TEMPO are shown in Figure 4. The $T_1$ relaxation rate of $H_2O@C_{60}$ in the presence of TEMPO is also shown for comparison purposes. The second-order relaxation coefficient, or relaxivity, $R_1$, was calculated using the following equation: $1/T_1 = 1/T_{1,0} + R_1[S]$. $T_{1,0}$ is the relaxation time in the absence of the paramagnetic relaxant, and [S] is the concentration of TEMPO. Similar measurements were carried out for $H_2@C_{60}$ and the related open-$C_{60}$ compounds $H_2$@K8′ and $H_2$@K13′. For solubility reasons the solvent employed was 1,2-dichlorobenzene-$d_4$ (Table 2).

As can be seen in Table 2, the values of $R_1$ are strikingly similar for four of the six *endo* fullerenes. The outliers, $H_2@C_{60}$ and $H_2O$@K13, correspond to the substantially

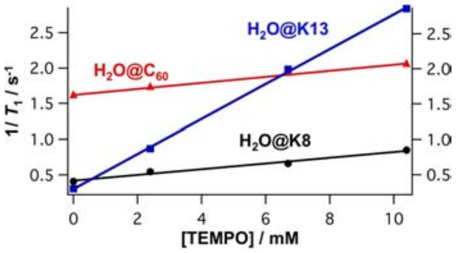

**Figure 4.** Relaxation rates ($1/T_1$) of $H_2O@C_{60}$, $H_2O@K8$, and $H_2O@K13$ in toluene-$d_8$ in the presence of TEMPO.

increased effectiveness of bimolecular relaxation by TEMPO. The origins of the relaxivity effect and its dependence on structure and dynamics have been analyzed in detail elsewhere.[5] It is possible that the good agreement of the values of $R_1$ for four of the fullerenes could arise from fortuitous cancellation of changes among the effective distances and lifetimes describing fullerene-nitroxide encounters. A simpler explanation is that the data show that these parameters are relatively insensitive to ring opening, solvent, or whether the *endo* molecule is $H_2O$ or $H_2$.

The larger than expected value of $R_1$ for $H_2@C_{60}$ with TEMPO is consistent with the earlier conclusion that its $R_1$ with the related nitroxide 4-oxo-TEMPO is larger than expected from reasonable estimates of the distance of closest approach and diffusive lifetimes.[5] No definitive explanation was offered then, although the suggestion of a weak complex or enhanced electron–nuclear coupling could not be ruled out.

**Case 4. Relaxivity induced by intermolecular interaction of nitroxide-fullerene complex.** The unexpectedly large $R_1$ for $H_2O@K13$, on the other hand, is consistent with the formation of a hydrogen-bonded complex formed via the attached OH groups. This enhancement does not occur, for example, with the open endo fullerenes $H_2O@K8$, $H_2@K8'$, or $H_2@K13'$ that do not have OH groups. Formation of such a complex would be expected to enhance the effectiveness of the paramagnet by extending the time during which the electron–nuclear dipolar interaction operates. Such inner-sphere relaxation effects have been known since the earliest days of magnetic resonance when they were first observed in water samples relaxed by paramagnetic transition metal ions.[10] Proton relaxation in a hydrogen bonded nitroxide complex has also been studied.[11]

In conclusion, we have measured the $T_1$ relaxation rates of *endo*-$H_2O$ in $H_2O@$Open-$C_{60}$ nitroxide derivatives, and $H_2O@$Open-$C_{60}$ in the presence of a relaxant TEMPO. The results are compared with those for an analogous series containing $H_2$. The results confirm that $T_1$ relaxation rates, relative to those readily achievable by intermolecular relaxation by TEMPO, are enhanced dramatically when the nitroxide radical is covalently attached to either the wall of the fullerene cage or to a functional group on the orifice of the Open-$C_{60}$. For example, achieving the relaxation rate of $H_2O@1$ ($1/T_{1,p} = 16\ s^{-1}$) intermolecularly using $H_2O@C_{60}$ and TEMPO ($R_1 = 43\ M^{-1}\ s^{-1}$) would require a paramagnet concentration of 0.37 M. The formation of hydrogen bonding between the nitroxide radical and the hydroxyl group on the orifice, however, enhances the magnitude of $R_1$ by a factor of approximately 6. This effect can be explained by formation of an inner sphere complex. It also suggests the possibility of further enhancing the effectiveness of intermolecular relaxation by changes in the structure of the relaxant, the fullerene, or the medium to take advantage of hydrogen-bonding, electrostatic, or steric interactions that may fine-tune the lifetime of the collision complex.

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**Supporting Information Available.** Synthesis and characterization of $H_2O@K13$-1. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.