# Distance-Dependent Paramagnet-Enhanced Nuclear Spin Relaxation of $H_2@C_{60}$ Derivatives Covalently Linked to a Nitroxide Radical

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ABSTRACT A series of $H_2@C_{60}$ derivatives covalently linked to a nitroxide radical has been synthesized. We report distance-dependent nuclear spin relaxivity of H_2 in these derivatives. The results clearly indicate that the relaxivity of H_2 is distance-dependent and in good agreement with the Solomon–Bloembergen equation, which predicts a $1/r^6$ dependence.

SECTION Kinetics, Spectroscopy
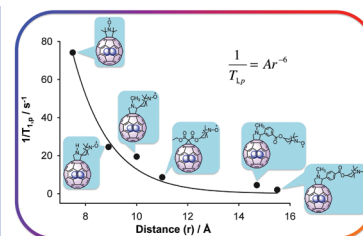
Nuclear spin relaxation of H_2 and its isotopomers has been extensively studied in the gas, liquid, and solid phases.[1,2] Recently, a few reports[3,4] of nuclear spin relaxation of H_2 in ordinary organic solvents have appeared. The discovery[5] that the hydrogen molecule can be encapsulated in the fullerene (C_{60}) cage leads to intriguing investigations to explore the interactions of the endohedral H_2 with the outside world.[6] Nuclear spin relaxation is a quantitative approach to probe these interactions. According to recent reports,[3,7] the relaxation times (T_1) are 10–20 times shorter for $H_2@C_{60}$ than those for H_2 in organic solvents. However, in the presence of paramagnetic relaxants, such as nitroxide radicals, the relaxation effect of the paramagnet is enhanced five-fold in $H_2@C_{60}$ compared to that for H_2 under the same conditions.[8] These results indicate that the hydrogen molecule in $H_2@C_{60}$ is not insulated from magnetic contact with the outside world.

Encapsulation of H_2 inside of C_{60} also enables us to take advantage of C_{60} chemical reactivity to covalently attach a paramagnet to the C_{60} cage,[9] which provides a platform for studying intramolecular spin relaxation of H_2 (so-called inner sphere proton relaxivity). According to the Solomon–Bloembergen equation,[10,11] the inner sphere relaxivity ($1/T_1$) is proportional to the reciprocal of the sixth power of the distance between the proton and the paramagnet centers. Most reports[12] on inner-sphere proton relaxivity are related to the first coordination sphere of complexes formed by water and paramagnetic metal ions. Due to the difficulty in obtaining a large range of accurate distance variations between the proton and the paramagnetic ion centers, there seems to have been no previous report of distance-dependent proton spin relaxation by the same kind of relaxant.

In the present investigation, we have synthesized a series of $H_2@C_{60}$ derivatives covalently linked to a nitroxide radical, as shown in Chart 1. By varying the spacers between C_{60} and the TEMPO functional groups, the calculated distance (by molecular modeling) between the encapsulated H_2 and the

nitroxide radical centers increases in the order from **1** to **6**. The derivative **7** consists of a nitroxide biradical substituent as a counterpart of the monoradical **4**. We report distance-dependent nuclear spin relaxation results for these $H_2@C_{60}$ nitroxide derivatives.

Derivatives **1**–**3** were synthesized using the well-known Prato reaction following literature procedures.[13–15] Synthesis of derivatives **4** and **7** was completed by the Bingle–Hirsh reaction following literature reports.[16] Details of the synthesis of derivatives **5** and **6** are given in the Supporting Information.

Nuclear spin relaxation times (T_1) were measured by the inversion–recovery method in argon-bubbled 1,2-dichloro-

Chart 1. Structures of $H_2@C_{60}$ Derivatives **1**–**7**[a]
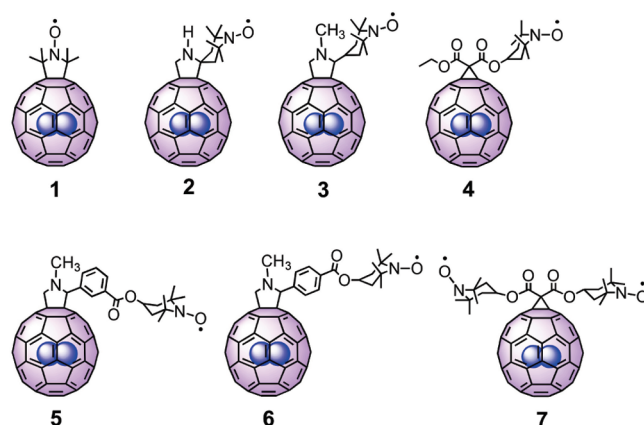
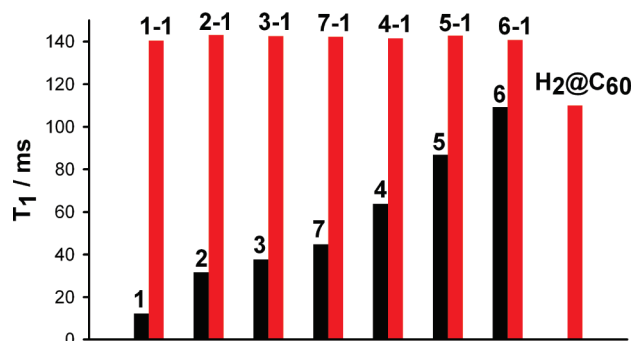[a] Blue balls indicate incarcerated H_2 or HD.

Figure 1. Nuclear spin relaxation times (T_1) of $H_2@C_{60}$ nitroxide derivatives **1–7** and its corresponding diamagnetic hydroxylamine derivatives (labeled as **1-1**, **2-1**, ..., **7-1**) in 1,2-dichlorobenzene-d_4 solutions at room temperature. Sample concentrations were ~2 mM. $H_2@C_{60}$ nitroxide derivatives are in black, and diamagnetic compounds are in red.

Table 1. Relaxation Rates ($1/T_{1,p}$) of $H_2@C_{60}$ Nitroxide Derivatives at RT and Distances between the Proton and the Nitroxide Radical Centers

	$T_{1,\text{obs}}$ (ms)[a]	$1/T_{1,p}$ (s^{-1})	distance[b] (estimated, Å)	distance[c] (calculated, Å)
1	12.3	74.2	7.5	$(7.5)^d$
2	31.7	24.5	8.9	9.0
3	37.7	19.5	10.0	9.4
4	63.8	8.6	11.0	10.7
5	86.9	4.5	14.7	12.0
6	109.2	2.1	15.5	13.6
7	44.8	15.3	11.0	

[a] In deoxygenated 1,2-dichlorobenzene-d_4. Sample concentrations were ~2 mM. [b] Distance from the center of the NO bond to the center of the fullerene, estimated from molecular models. [c] Distance calculated based on $1/T_{1,p}$ values. [d] Assumed to be the same as the estimated distance by molecular models.

benzene-d_4 solutions of **1–7** and their hydroxylamine derivatives at room temperature. The concentrations of all samples were ~2 mM. The hydroxylamine derivatives were synthesized by treatment of the corresponding $H_2@C_{60}$ nitroxide with phenylhydrazine (eq 1).[9] In eq 1, R represents any groups between C_{60} and the TEMPO moiety in **1–7**. Note that the $H_2@C_{60}$ hydroxylamine derivatives can be reoxidized to the corresponding nitroxides by treatment with copper acetate,[17] a transition from diamagnetic to paramagnetic species.

$$(1)$$
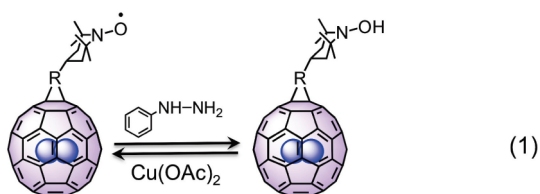
As shown in Figure 1 (data shown in Table 1), T_1 values increase from **1** to **6** with increasing distance between the encapsulated H_2 and the unpaired electron. The T_1 value of the biradical–derivative **7** is about two-thirds of the T_1 value of its monoradical counterpart **4**. The values of T_1 of the diamagnetic derivatives (labeled as **1-1**, ...,**7-1**) do not change with substituents and are ~30 ms longer than that for $H_2@C_{60}$. This is consistent with a shorter correlation time for rotational motion of H_2 within the modified cages,[3] as might be expected from a weak breaking of the nearly spherical symmetry of C_{60} by the substituents. In addition, the relaxivity of HD in the derivative **1** is similar to that for H_2 in **1**, indicating that the electron–nuclear interaction overrides other relaxation mechanisms. Similar results have been obtained for HD relaxivity induced by TEMPO in $HY@C_{60}$ (Y = H or D) and in an open-cage derivative (unpublished results). For derivative **6** with the longest estimated distance in the series, its T_1 value is close to that of $H_2@C_{60}$. However, considering the longer T_1 value of its diamagnetic counterpart (~140 ms), the nitroxide radical of derivative **6** is still in the effective range. To test the possibility of a contribution to the H_2 relaxivity by intermolecular interactions, T_1 values of derivatives **1–6** were obtained in 10 mM solutions. The

increase of H_2 relaxivity was less than 5%, indicating that contribution by intermolecular interactions is not significant. Because of its larger magnetic moment, the intermolecular interaction would be expected to be enhanced for biradical, **7**. It would therefore be expected to produce faster relaxation than expected, based on the monoradical **4**, rather than the somewhat slower rate that is observed.

It is well-known[12] that inner-sphere proton relaxivity theory may be applied to explain intramolecular proton relaxation, for example, water proton relaxivity induced by the first coordination sphere of Cu(II) and Gd(III) hydrates.[11] Two types of contributions to inner-sphere relaxation are contact and dipole–dipole mechanisms. The contribution from the contact mechanism has been found to be negligible in the case of intermolecular relaxation by nitroxides.[18,19] The relaxivity, $1/T_{1,p} = (1/T_{1,\text{obs}} - 1/T_{1,d})$, due to the electron–nuclear dipole–dipole interaction is computed using the Solomon–Bloembergen equation (eq 2, SI units), where $T_{1,p}$ is the relaxation time caused by the paramagnetic species, $T_{1,\text{obs}}$ is the observed relaxation time, and $T_{1,d}$ is the relaxation time in the absence of the paramagnetic center, that is, the hydroxyamine derivatives in the current system, γ_I is magnetogyric ratio of the nucleus that is being relaxed (H), g is the electronic g factor, μ_B is the Bohr magneton, r is the distance between the proton and the unpaired electron in the complex, ω_I and ω_S are the nuclear and electronic Larmor frequencies, respectively, and τ_c is the global correlation time.

$$\frac{1}{T_{1,\text{p}}} = \frac{2}{15}\left(\frac{\mu_0}{4\pi}\right)^2 \left[\frac{\gamma_I^2 g^2 \mu_B^2 S(S+1)}{r^6}\right]\left[\frac{3\tau_c}{1+\omega_I^2\tau_c^2} + \frac{7\tau_c}{1+\omega_S^2\tau_c^2}\right]$$
$$= \frac{A}{r^6} \qquad (2)$$

According to eq 2, the relaxation rate due to the presence of the paramagnet should be proportional to r^{-6}, τ_c, and $S(S+1)$ (the value of spin quantum number $S = 1/2$ for **1–6**). We can test each of these parameters as follows.

If it is assumed that variations in the group attached to the C_{60} cage have only a small effect on the rotational correlation time of the cage, τ_c, it is reasonable to expect that $1/T_{1,p}$ varies
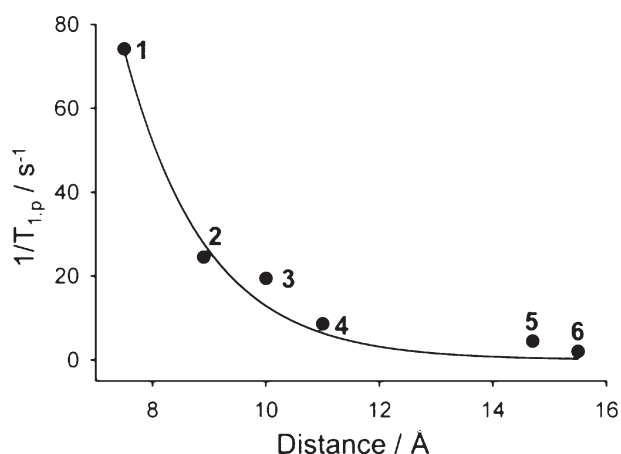
Figure 2. $1/T_{1,p}$ versus calculated distances from molecular modeling of $H_2@C_{60}$ nitroxide derivatives **1−6**.

as r^{-6}. Since compound **1** is likely to be the most stereochemically rigid structure, we assume that the value of r obtained from molecular modeling is a good approximation to the true value. Figure 2 shows a plot (solid line) of $1/T_{1,p}$ versus estimates of r, scaled to the values for **1**. It is clear that the fit is remarkably good over a 2-fold variation in the estimated values of r. Conversely, one can obtain estimates for calculated values of r from the intersection of the values of $1/T_{1,p}$ with the calculated curve. These values are shown in Table 1. For derivatives **3−6**, the calculated values of r based on $1/T_{1,p}$ is consistently shorter than those obtained from molecular modeling, suggesting that more compacting conformations are preferred in these nonrigid structures.[20] Furthermore, the value of r^{-6} in eq 2, because of the nature of the dipolar interaction, is actually related to the average over internal motions of the inverse of r^{-3} by $r^{-6} = \langle r^{-3} \rangle^2$. Attempts to explain the small discrepancies in Figure 2 would need to take this into account.

An attempt to calculate the value of $1/T_{1,p}$ for **1** using the calculated distance by molecular modeling in eq 2 leads to the interesting conclusion that there is no value of τ_c which can give a value of $1/T_{1,p}$ as large as that observed! This disparity might be explained either by the true value of r for **1** being somewhat smaller than the calculated value or by a small additional contribution to T_1 from scalar coupling. Independent estimates of τ_c and r would be required to test these possibilities. This limit is imposed by the first term in eq 2, which has a maximum value when $\omega_I \tau_c = 1$, or in the present case for 500 MHz ^{1}H NMR, $\tau_c = 318$ ps. The values of r obtained using this estimate of τ_c for all of the fullerene nitroxides are smaller by ~ 0.2 Å than those based on compound **1**. Fitting to values of τ_c either smaller or larger than 318 ps would require even smaller values of r.

If it is then assumed that $\tau_c = 3.2 \times 10^{-10}$ s is a reasonable estimate of the correlation time and does not vary significantly within the series **1−6**, the Stokes−Debye−Einstein equation, $\tau_c = (4\pi/3) r_{SDE}^3 \eta / k_B T$ may then be used, along with the viscosity of the solvent,[3] to estimate an average effective radius, r_{SDE}, for the modified fullerenes. The result obtained, $r_{SDE} = 6.2$ Å, is, as expected, only somewhat larger than estimates of the van der Waals radius of C_{60}, ~ 5.0 Å,[21] and

serves to confirm the applicability of eq 2. The agreement between the observed and expected value of τ_c based on the simple dipolar model of eq 2 also indicates a negligible contribution in this case from electron spin relaxation.[11] This is consistent with the value of T_1 for the nitroxide electron spin, which is expected to be $\sim 10^{-6}$ seconds,[22] that is, much longer than the correlation time for rotation of the fullerene and ineffective in contributing to the dipolar mechanism.[11]

Comparison of $1/T_{1,p}$ for the biradical **7** with that of the closely related radical **4** has been used to test the dependence on electron spin. It is seen from Table 1 that the corresponding relaxation rates are in the ratio of 1.8:1. The hyperfine pattern of the EPR spectrum of **7** (see Supporting Information) is consistent with a weak coupling of the two unpaired electrons.[23] Under these conditions, one expects the biradical to be twice as effective as the monoradical[8] since the biradical is, in effect, acting as an $S = 1/2$ spin system at twice the concentration, in approximate agreement with the observed ratio. A concentration-dependent T_1 measurement shows that an increase of the relaxivity of **7** at 10 mM is less than 5%, once again indicating that contribution from intermolecular interactions is negligible.

In summary, a series of $H_2@C_{60}$ derivatives covalently linked to a nitroxide radical has been synthesized. A clear distance-dependent nuclear spin relaxation of H_2 in these derivatives has been observed and is in good agreement with the inner-sphere proton relaxivity theory. The data can be fitted using the Solomon−Bloembergen equation, giving good agreement with the expected $1/r^6$ dependence on distance and yielding a reasonable value of the correlation time, τ_c, for rotation of the C_{60} derivatives. Application of this series of compounds to the related study of paramagnet-enhanced para−ortho conversion of H_2 in $H_2@C_{60}$ nitroxide derivatives[9,24] is currently under investigation.

SUPPORTING INFORMATION AVAILABLE Synthesis of derivatives **5** and **6**, and experimental details including the EPR spectrum of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Gaines, J. R.; Souers, P. C. The Spin-Lattice Relaxation Time (T_1) in Mixtures of Hydrogen Isotopes. *Adv. Magn. Reson.* **1988**, *12*, 91–112.

(2) Deutsch, J. M.; Oppenheim, I. Nuclear Relaxation in Hydrogen Gas and Liquid. *Adv. Magn. Reson.* **1966**, *2*, 225–262.

(3) Sartori, E.; Ruzzi, M.; Turro, N. J.; Decatur, J. D.; Doetschman, D. C.; Lawler, R. G.; Buchachenko, A. L.; Murata, Y.; Komatsu, K. Nuclear Relaxation of H_2 and $H_2@C_{60}$ in Organic Solvents. *J. Am. Chem. Soc.* **2006**, *128*, 14752–14753.

(4)   Aroulanda, C.; Starovoytova, L.; Canet, D. Longitudinal Nuclear Spin Relaxation of *Ortho*- and *Para*-Hydrogen Dissolved in Organic Solvents. *J. Phys. Chem. A* **2007**, *111*, 10615–10624.

(5)   Komatsu, K.; Murata, M.; Murata, Y. Encapsulation of Molecular Hydrogen in Fullerene C_{60} by Organic Synthesis. *Science* **2005**, *307*, 238–240.

(6)   Turro, N. J.; Chen, J. Y.-C.; Sartori, E.; Ruzzi, M.; Martí, A.; Lawler, R.; Jockusch, S.; Lopez-Gejo, J.; Komatsu, K.; Murata, Y. The Spin Chemistry and Magnetic Resonance of $H_2@C_{60}$. From the Pauli Principle to Trapping a Long Lived Nuclear Excited Spin State Inside a Buckyball. *Acc. Chem. Res.* **2010**, *43*, 335–345.

(7)   Chen, J. Y.-C.; Martí, A. A.; Turro, N. J.; Komatsu, K.; Murata, Y.; Lawler, R. G. Comparative NMR Properties of H_2 and HD in Toluene-d_8 and in $H_2/HD@C_{60}$. *J. Phys. Chem. B* In press.

(8)   Sartori, E.; Ruzzi, M.; Turro, N. J.; Komatsu, K.; Murata, Y.; Lawler, R. G.; Buchachenko, A. L. Paramagnet Enhanced Nuclear Relaxation of H_2 in Organic Solvents and in $H_2@C_{60}$. *J. Am. Chem. Soc.* **2008**, *130*, 2221–2225.

(9)   Li, Y.; Lei, X.; Jockusch, S.; Chen, J. Y.-C.; Frunzi, M.; Johnson, J. A.; Lawler, R. G.; Murata, Y.; Murata, M.; Komatsu, K.; Turro, N. J. A Magnetic Switch for Spin-Catalyzed Interconversion of Nuclear Spin Isomers. *J. Am. Chem. Soc.* **2010**, *132*, 4042–4043.

(10) Solomon, I. Relaxation Processes in a System of Two Spins. *Phys. Rev.* **1955**, *99*, 559–565.

(11) Bloembergen, N.; Morgan, L. O. Proton Relaxation Times in Paramagnetic Solutions. Effects of Electron Spin Relaxation. *J. Chem. Phys.* **1961**, *34*, 842–850.

(12) Toth, E; Helm, L.; Merbach, A. E. Relaxivity of MRI Contrast Agents. *Top. Curr. Chem.* **2002**, *221*, 62–101.

(13) Schick, G.; Levitus, M.; Kvetko, L.; Johnson, B. A.; Lamparth, I.; Lunkwitz, R.; Ma, B.; Khan, S. I.; Garcia-Garibay, M. A.; Rubin, Y. Unusual Luminescence of Hexapyrrolidine Derivatives of C_{60} with T_h and Novel D_3-Symmetry. *J. Am. Chem. Soc.* **1999**, *121*, 3246–3247.

(14) Mazzoni, M.; Franco, L.; Ferrarini, A.; Corvaja, C.; Zordan, G.; Scorrano, G.; Maggini, M. Unexpected High Ordering of a [60]Fullerene Nitroxide in the Nematic Phase of 4-4′-Azoxyanisole. *Liq. Cryst.* **2002**, *29*, 203–208.

(15) Arena, F.; Bullo, F.; Conti, F.; Corvaja, C.; Maggini, M.; Prato, M.; Scorrano, G. Synthesis and EPR Studies of Radicals and Biradical Anions of C_{60} Nitroxide Derivatives. *J. Am. Chem. Soc.* **1997**, *119*, 789–795.

(16) Gubskaya, V. P.; Berezhnaya, L. S.; Gubaidullin, A. T.; Faingold, I. I.; Kotelnikova, R. A.; Konovalova, N. P.; Morozov, V. I.; Litvinov, I. A.; Nuretdinov, I. A. Synthesis, Structure and Biological Activity of Nitroxide Malonate Methanofullerenes. *Org. Biomol. Chem.* **2007**, *5*, 976–981.

(17) Lee, T. D.; Keana, J. F. W. In Situ Reduction of Nitroxide Spin Labels with Phenylhydrazine in Deuteriochloroform Solution. A Convenient Method for Obtaining Structural Information on Nitroxides Using Nuclear Magnetic Resonance Spectroscopy. *J. Org. Chem.* **1975**, *40*, 3145–3147.

(18) Borah, B.; Bryant, R. G. NMR Relaxation Dispersion in an Aqueous Nitroxide System. *J. Chem. Phys.* **1981**, *75*, 3297–3300.

(19) Bates, R. D.; Drozdoski, W. S. Use of Nitroxide Spin Labels in Studies of Solvent−Solute Interactions. *J. Chem. Phys.* **1977**, *67*, 4038–4044.

(20) An alternative would be to ascribe deviations from the calculated curve to variations in τ_c. Unfortunately, a choice of deviations based on r or τ_c cannot be made using the data given here. However, if $\omega_I \tau_c \approx 1$, as seems, in the present study, to be consistent with the analysis given below, measuring the T_1's at more than one magnetic field should make it possible to separately evaluate r and τ_c. Alternatively, related values of τ_c for rotational motion centered on the unpaired electron may be obtained by measuring the electron relaxation time in each of the nitroxides. Such studies are in progress. The preliminary results indicate that τ_c is somewhat shorter than 3×10^{-10} s and varies no more than 2-fold over the series **1**−**6**.

(21) Bakale, G.; Lacmann, K.; Schmidt, W. F. C_{60} and C_{70} Fullerene Ions in Nonpolar Liquids: Mobility and Radiation-Chemical Changes. *J. Phys. Chem.* **1996**, *100*, 12477–12482.

(22) Hwang, J. S.; Mason, R. P.; Hwang, L.-P.; Freed, J. H. Electron Spin Resonance Studies of Anisotropic Rotational Reorientation and Slow Tumbling in Liquid and Frozen Media. III. Perdeuterated 2,2,6,6-Tetramethyl-4-piperidone *N*-Oxide and an Analysis of Fluctuating Torques. *J. Phys. Chem.* **1975**, *79*, 489–511.

(23) Glarum, S. H.; Marshall, J. H. Spin Exchange in Nitroxide Biradicals. *J. Chem. Phys.* **1967**, *47*, 1374–1378.

(24) Turro, N. J.; Martí, A. A.; Chen, J. Y.-C.; Jockusch, S.; Lawler, R. G.; Ruzzi, M.; Sartori, E.; Chuang, S.-C.; Komatsu, K.; Murata, Y. Demonstration of a Chemical Transformation Inside a Fullerene. The Reversible Conversion of the Allotropes of $H_2@C_{60}$. *J. Am. Chem. Soc.* **2008**, *130*, 10506–10507.