Distance-Dependent Paramagnet-Enhanced Nuclear Spin Relaxation of H₂@C₆₀ Derivatives Covalently Linked to a Nitroxide Radical

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Abstract A series of H₂@C₆₀ derivatives covalently linked to a nitroxide radical has been synthesized. We report distance-dependent nuclear spin relaxivity of H₂ in these derivatives. The results clearly indicate that the relaxivity of H₂ is distance-dependent and in good agreement with the Solomon–Bloembergen equation, which predicts a 1/ᵣ⁻⁶ dependence.

Nuclear spin relaxation of H₂ and its isotopomers has been extensively studied in the gas, liquid, and solid phases. Recently, a few reports of nuclear spin relaxation of H₂ in ordinary organic solvents have appeared. The discovery that the hydrogen molecule can be encapsulated in the fullerene (C₆₀) cage leads to intriguing investigations to explore the interactions of the endohedral H₂ with the outside world. Nuclear spin relaxation is a quantitative approach to probe these interactions. According to recent reports, the relaxation times (T₁) are 10–20 times shorter for H₂@C₆₀ than those for H₂ 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 H₂@C₆₀ compared to that for H₂ under the same conditions. These results indicate that the hydrogen molecule in H₂@C₆₀ is not insulated from magnetic contact with the outside world.

Encapsulation of H₂ inside of C₆₀ also enables us to take advantage of C₆₀ chemical reactivity to covalently attach a paramagnet to the C₆₀ cage, which provides a platform for studying intramolecular spin relaxation of H₂ (so-called inner sphere proton relaxivity). According to the Solomon–Bloembergen equation, the inner sphere relaxivity (1/T₁) is proportional to the reciprocal of the sixth power of the distance between the proton and the paramagnet centers. Most reports 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 H₂@C₆₀ derivatives covalently linked to a nitroxide radical, as shown in Chart 1. By varying the spacers between C₆₀ and the TEMPO functional groups, the calculated distance (by molecular modeling) between the encapsulated H₂ 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 H₂@C₆₀ nitroxide derivatives.

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

Nuclear spin relaxation times (T₁) were measured by the inversion–recovery method in argon-bubbled 1,1,2-dichloro-

Chart 1. Structures of H₂@C₆₀ Derivatives 1–7

†Blue balls indicate incarcerated H₂ or HD.

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benzene-\(d_4\) solutions of 1−7 and their hydroxylamine derivatives at room temperature. The concentrations of all samples were \(\sim 2\) mM. The hydroxylamine derivatives were synthesized by treatment of the corresponding \(\text{H}_2@\text{C}_{60}\) nitroxide with phenylhydrazine (eq 1).9 In eq 1, \(R\) represents any groups between \(\text{C}_{60}\) and the TEMPO moiety in 1−7. Note that the \(\text{H}_2@\text{C}_{60}\) hydroxylamine derivatives can be reoxidized to the corresponding nitroxides by treatment with copper acetate,17 a transition from diamagnetic to paramagnetic species.

As shown in Figure 1 (data shown in Table 1), \(T_1\) values increase from 1 to 6 with increasing distance between the encapsulated \(\text{H}_2\) 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, 2-1, ..., 7-1) do not change with substituents and are \(\sim 50\) ms longer than that for \(\text{H}_2@\text{C}_{60}\). This is consistent with a shorter correlation time for rotational motion of \(\text{H}_2\) within the modified cages,3 as might be expected from a weak breaking of the nearly spherical symmetry of \(\text{C}_{60}\) by the substituents. In addition, the relaxation of HD in the derivative 1 is similar to that for \(\text{H}_2\) in 1, indicating that the electron−nuclear interaction overrides other relaxation mechanisms. Similar results have been obtained for HD relaxation induced by TEMPO in \(\text{HY@C}_{60}\) (\(Y = \text{H}\) 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 \(\text{H}_2@\text{C}_{60}\). However, considering the longer \(T_1\) value of its diamagnetic counterpart (\(\sim 140\) ms), the nitroxide radical of derivative 6 is still in the effective range. To test the possibility of a contribution to the \(\text{H}_2\) relaxation by intermolecular interactions, \(T_1\) values of derivatives 1−6 were obtained in 10 mM solutions. The increase of \(\text{H}_2\) 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-known12 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 \(\text{Cu}^{2+}\) and \(\text{Gd}^{3+}\) hydrates.11 Two types of contributions to inner-sphere relaxations are contact and dipole−dipole mechanisms. The contact contribution has been found to be negligible in the case of intermolecular relaxation by nitroxides.18,19 The relaxivity, \(1/T_{1,p} = (1/T_{1,obs} - 1/T_{1,d})\), due to the electron−nuclear dipole−dipole interaction is computed using the Solomon−Bloembergen equation (eq 2). However, where \(T_{1,p}\) is the relaxation time caused by the paramagnetic species, \(T_{1,obs}\) is the observed relaxation time, and \(T_{1,d}\) is the relaxation time in the absence of the paramagnetic center, that is, the hydroxylamine derivatives in the current system. \(\gamma_1\) is the magnetic moment, \(I\) is the nuclear gyromagnetic ratio of the nucleus that is being relaxed, \(\omega_1\) and \(\omega_S\) are the nuclear and electronic Larmor frequencies, respectively, and \(r_{c}\) is the global correlation time.

\[
\frac{1}{T_{1,p}} = \frac{2}{15} \left( \frac{\mu_0}{4\pi} \right)^2 \gamma_1^2 I^2 g_1^2 g_S^2 \left( S + 1 \right) \left[ \frac{5\tau_c}{1 + \omega_1^2 \tau_c^2} + \frac{7\tau_c}{1 + \omega_S^2 \tau_c^2} \right]
\]

According to eq 2, the relaxation rate due to the presence of the paramagnet should be proportional to \(r^{-6}\), \(\tau_c\), 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 \(\text{C}_{60}\) cage have only a small effect on the rotational correlation time of the cage, \(\tau_c\), it is reasonable to expect that \(1/T_{1,p}\) varies

<table>
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<th>(T_{1,obs}) (ms)</th>
<th>(1/T_{1,p}) (s(^{-1}))</th>
<th>(\text{distance}) (estimated, Å)</th>
<th>(\text{distance}) (calculated, Å)</th>
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<tr>
<td>5</td>
<td>86.9</td>
<td>4.5</td>
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</tr>
<tr>
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<td>15.5</td>
</tr>
<tr>
<td>7</td>
<td>44.8</td>
<td>15.3</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*In deoxygenated 1,2-dichlorobenzene-\(d_4\). Sample concentrations were \(\sim 2\) mM. *Distance from the center of the NO bond to the center of the fullerene, estimated from molecular models. *Distance calculated based on \(1/T_{1,p}\) values. The molecule should be proportional to \(r^{-6}\) and \(S(S + 1)\).
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. Furthermore, the value of $r^{-6}$ in eq 2, because of the nature of the dipolar interaction, is actually linked to the average over internal motions of the inverse of $r^{-3}$ by $r^{-6} = (r^{-3})^2$. 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 $r_c$ 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 $r_c$ 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 $\alpha r_c = 1$, or in the present case for 500 MHz $^1$H NMR, $r_c = 318$ ps. The values of $r$ obtained using this estimate of $r_c$ for all of the fullerene nitroxides are smaller by $\sim 0.2$ Å than those based on compound 1. Fitting to values of $r_c$ either smaller or larger than 318 ps would require even smaller values of $r$.

If it is then assumed that $r_c = 5.2 \times 10^{-10}$ s is a reasonable estimate of the correlation time and does not vary significantly within the series 1–6, the Stokes–Debye–Einstein equation, $\tau_c = (4\pi/3)\eta r_{\text{SDE}}^3 M/\rho$ may then be used, along with the viscosity of the solvent, to estimate an average effective radius, $r_{\text{SDE}}$, for the modified fullerenes. The result obtained, $r_{\text{SDE}} = 6.2$ Å, is, as expected, only somewhat larger than estimates of the van der Waals radius of C$_{60}$, $\sim 5.0$ Å, and serves to confirm the applicability of eq 2. The agreement between the observed and expected value of $\tau_c$ based on the simple dipolar model of eq 2 also indicates a negligible contribution in this case from electron spin relaxation. This is consistent with the value of $T_1$ for the nitroxide electron spin, which is expected to be $\sim 10^{-10}$ seconds, that is, much longer than the correlation time for rotation of the fullerene and ineffective in contributing to the dipolar mechanism.

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. Under these conditions, one expects the biradical to be twice as effective as the monoradical 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 $1/T_{1,p}$ dependence on distance and yielding a reasonable value of the correlation time, $\tau_c$, 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 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**


(20) An alternative would be to ascribe deviations from the calculated curve to variations in T_{2}. Unfortunately, a choice of deviations based on r or T_{2} cannot be made using the data given here. However, if δω_{T_{2}} ≈ 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 T_{2}. Alternatively, related values of T_{2} 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 T_{2} is somewhat shorter than 3 × 10^{-10}s and varies no more than 2-fold over the series 1–6.