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Synthesis and characterization of bispyrrolidine derivatives of $H_2@C_{60}$: differentiation of isomers using 1H NMR spectroscopy of endohedral H_2 †Yongjun Li,^a Xuegong Lei,^a Ronald G. Lawler,^b Yasujiro Murata,^c Koichi Komatsu^d and Nicholas J. Turro^{*a}

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Bisadduct isomers of a $H_2@C_{60}$ derivative with nitroxide addends have been synthesized, isolated and characterized. The 1H NMRs of endohedral H_2 of the major isomers show well-separated chemical shifts, which could be useful for structural assignment and identification of the purity of the C_{60} bisadduct isomers.

Monoadducts of fullerene (C_{60}) predominantly occur in its (6,6) double bonds shared by two six-membered rings due to their electron-deficient alkene-like character.¹ Many C_{60} mono-derivatives have been synthesized and well-known synthetic methods, such as the synthesis of C_{60} malonate derivatives (Bingle–Hirsch reaction)² and C_{60} pyrrolidine derivatives (Prato reaction)³ have been established. By using less than one equivalent of reagent, monoadducts can be obtained in moderate to high yields by chromatographic separation from unreacted starting materials and traces of multiple adducts. If more than one equivalent of reagent is employed, one can obtain C_{60} bisadduct isomers in moderate yield along with the monoadduct.

A total of eight C_{60} bisadduct isomers⁴ are possible with symmetrical substituents (Fig. 1): three *cis*-isomers, four *trans*-isomers and one *equatorial*-isomer. Structural assignments for different isomers are usually based on a combination of HPLC retention times (polarity), UV-Vis spectroscopy and 1H or ^{13}C NMR spectroscopy.⁵ However, due to the complexity of the bisadducts, it is difficult to unambiguously assign isomer structures. Cross and coworkers⁶ demonstrated the elegant use of 3He NMR spectroscopy to differentiate some of the isomers of $^3He@C_{60}$ bisadducts. Transient EPR spectroscopy of C_{60} triplet excited state was also used to differentiate the C_{60} bisadduct isomers.⁷ Recently, Mazzoni and coworkers⁸ reported synthesis and EPR study of C_{60} pyrrolidine

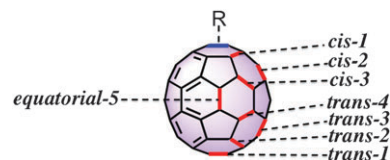


Fig. 1 C_{60} bisadduct isomers relative to the first addend R.

bisadducts with nitroxide addends. Due to line broadening caused by nitroxide radicals, structure assignment of these nitroxide isomers based on 1H NMR spectroscopy is very difficult. However, a comparison of the UV-Vis spectra with reported diamagnetic precursors proved to be effective and served as a basis to relatively safely assign all five major isomers.

We have been interested in the synthesis of $H_2@C_{60}$ and $H_2@C_{60}$ derivatives covalently linked to a nitroxide radical.⁹ The mono-addition of a nitroxide radical to $H_2@C_{60}$ shifts the 1H NMR of endohedral H_2 from ~ -1.4 ppm to ~ -4.3 ppm, a very significant ~ 3 ppm upfield shift.¹⁰ The sensitivity of the chemical shift of endohedral H_2 caused by the outside substituents provides a possibility to differentiate the $H_2@C_{60}$ bisadduct isomers. Such a method would be very useful for both structure assignment and identification of the purity of the isomers. In particular, this would be important for structural characterization of $H_2@C_{60}$ nitroxide derivatives, in which 1H NMR of the substituted region becomes more overlapped due to effects from the unpaired electrons.

We report the synthesis, separation and characterization of the major bisadduct isomers of a $H_2@C_{60}$ derivative with nitroxide addends (**1**, Fig. 2). Chemical shifts of endohedral H_2 of the bisadducts are well separated and have been assigned to each isomer. As part of the characterization strategy, we also compared 1H NMR spectra of endohedral H_2 of **1** with that of the structurally established bisadducts of a $H_2@C_{60}$

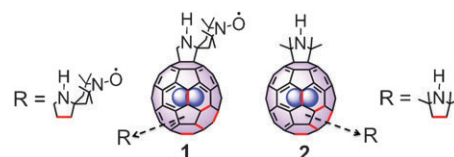


Fig. 2 $H_2@C_{60}$ bisadduct isomers of **1** and **2**. Blue balls indicate a mixture of encapsulated H_2 and HD.

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diamagnetic derivative (**2**, Fig. 2). Because of the availability of a mixture of isotopomers of $H_2@C_{60}$, the starting material for synthesizing **1** and **2** is a mixture of $H_2@C_{60}$ and $HD@C_{60}$, where the $HD@C_{60}$ serves as an excellent internal standard for previous 1H NMR analysis.¹⁰

Compounds **1** and **2** were synthesized following literature procedures.^{8,11} Fortunately, the difference of the polarity of the isomers of **1** is sufficient to allow acceptable separation of four of the five major isomers using preparative TLC. Due to the low yield of the *trans*-1 isomer, we were only able to isolate and characterize this isomer using the larger available quantities of C_{60} as the starting material. The separation of the bisadduct isomer mixture of **2** from its *mono*- and *tri*- or higher adducts was accomplished by column chromatography. No attempts were made to separate each isomer of **2** by HPLC. Detailed synthesis and separation conditions are provided in ESI†. The isomeric nature of the bisadducts of **1** and **2** was confirmed by mass spectrometry.

Due to asymmetrical additions to the C_{60} cage, each bisadduct isomer of **1** also gives several geometrical isomers¹² caused by orientation change of the substituents: three possible isomers for *trans*-2, *trans*-3 and *trans*-4 (see Fig. S1 in ESI†) and two possible isomers for *trans*-1 and equatorial-5 (*e*-5).

As reported,^{8,12} comparison of the UV-Vis spectra between 400 and 700 nm region allowed the correlative assignment of structures of the five isomers of **1** (see Fig. S2–Fig. S6 in ESI†). As further support of the assignments, the elution order of the five isomers is *trans*-1, *trans*-2, *trans*-3, *trans*-4 and *e*-5, which matches the elution order of C_{60} malonate bisadducts reported by Hirsch *et al.*⁴

The 1H NMR spectrum of endohedral H_2 and HD of a mixture of the four isomers from **1** is shown in Fig. 3a. The individual 1H NMR spectrum of each isomer is given in ESI†.

A few salient features can be extracted from the NMR spectrum of **1**. First, the NMR peaks for the endohedral protons are all well upfield from TMS and therefore well outside the range of chemical shifts for the external protons. Second, H_2 and HD peaks of each isomer overlap due to the broadening effects of the two radicals. Third, the individual NMR spectra of *trans*-3 and *e*-5 isomers (see Fig. S8 and Fig. S10 in ESI†) show slightly separated upfield chemical shifts with *trans*-3. However, the isomer mixture shows only one broad peak, indicating that the effects from unpaired electrons override the small difference of the chemical shifts between *trans*-3 and *e*-5 isomers.

One strategy to eliminate the broadening effects from unpaired electrons is to reduce the nitroxide to a corresponding diamagnetic species, such as its hydroxylamine.¹⁰ Therefore, we treated the isomer mixture with phenylhydrazine and obtained the associated NMR spectra of the hydroxylamine bisadducts. As expected, the NMR of the latter exhibited sharp signals for H_2 (singlet) and HD (triplet). Fig. 3b shows the NMR spectrum of the bisadducts of the hydroxylamine in the region of *trans*-3 and *e*-5. The H_2 and HD signals of reduced *trans*-3 and *e*-5 are indicated by red and blue arrows, respectively. NMR signals of products from reduction of one of the two radicals also appear as shoulders on the left of completely reduced ones. The 1H NMR spectrum of completely reduced *trans*-3 by phenylhydrazine shows one set of H_2

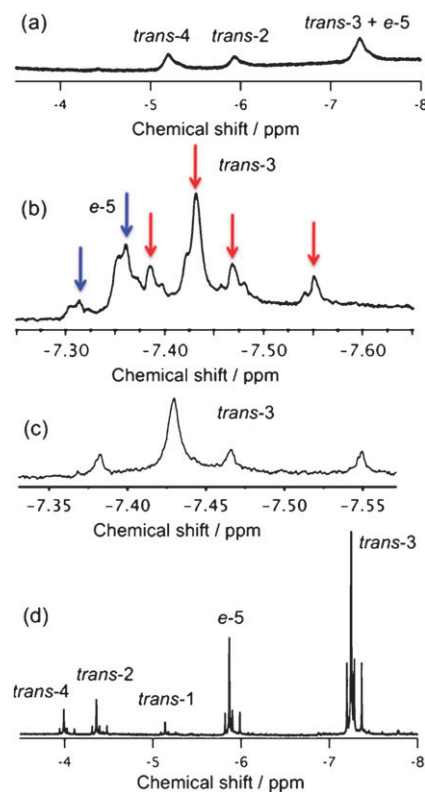


Fig. 3 1H NMR spectra of bisadduct isomers in 1,2-dichlorobenzene- d_4 solutions. (a) A mixture of four isomers of **1**; (b) The mixture of isomers of **1** after treatment with phenylhydrazine; (c) The *trans*-3 isomer of **1** after treatment with phenylhydrazine; (d) A mixture of five isomers of **2**.

and HD signals (Fig. 3c), demonstrating that either geometrical isomers caused by orientation change of the substituents are indistinguishable or only one geometrical isomer exists as the major product. The chemical shifts among the isomers encompass ~ 2 ppm. By comparison with reported 3He NMR of *N*-methylpyrrolidine- C_{60} bisadduct,⁶ chemical shifts of *trans*-3, *trans*-4 and *trans*-2 match the order of 3He NMR. The 1H NMR spectrum of the isomer mixture of the diamagnetic derivative **2** clearly shows H_2 and HD signals of five major isomers (Fig. 3d). By analogy, the chemical shifts of five isomers of **2** were assigned and integration of each peak provides the relative yield of each isomer, which is consistent with reported yields with *trans*-3 (highest yield) to *trans*-1 (lowest yield).⁸ The large difference of the chemical shifts of endohedral H_2 in the bisadduct isomers is possibly attributed to the small variations in the ring currents on the fullerene surface caused by the changes of addition orientation as observed on the endohedral 3He NMR.⁶

EPR spectra of all five isomers of **1** in deoxygenated toluene solutions at room temperature show a typical 3-line feature with coupling constant $a_N = 15$ G, which indicates that the electron exchange constant (J) is $\ll a_N$ (see Fig. S11–Fig. S15 in ESI†).^{12,13} This is expected since the distances¹² between the two radical sites are considerably larger than those in the corresponding methylpyrrolidine biradicals⁸ for which $J \geq a_N$.

Despite the small value of J , there is still the possibility that some evidence of interaction between the two unpaired

Table 1 Elution order and EPR linewidths of isomers of **1** and the mononitroxide

Order of elution of 1	Isomer	EPR linewidths ($\Delta H_{1/2}$, G, $m_N = +1$)
1	<i>mono</i>	2.0 (1.1) ^a
2	<i>trans-1</i>	3.1 (2.6)
3	<i>trans-2</i>	3.0 (3.0)
4	<i>trans-3</i>	3.6 (2.7)
5	<i>trans-4</i>	4.1 (2.4)
6	<i>e-5</i>	3.9 (2.8)

^a Difference in linewidth, Δ , between the high- and low-field peaks. Estimated error ± 0.2 G.

electrons could manifest itself through excess broadening of the solution EPR lines by through-space dipolar coupling. Such weak dipolar coupling was inferred from simulations of the EPR of frozen solutions of *trans-3* and *e-5* derivatives of C₆₀.¹² Inspection of the six EPR spectra of monoadduct and bisadducts at 213 K (see Fig. S16 in ESI†) reveals that the peaks from the biradicals are indeed broader than those of the mononitroxide. There is also a significantly larger difference in width between the low- and high-field lines in the biradicals than in the mononitroxide.

The linewidth differences were quantified by estimating the full-width at half-height, $\Delta H_{1/2}$, corresponding to the absorption peak for each of the three hyperfine lines using simulations to correct the observed derivative-full-widths for the effects of field modulation¹⁴ and possibly unresolved hyperfine coupling from the 12 methyl protons.^{15,16} The widths of the low-field ($m_N = +1$), narrowest, lines for each of the isomers, are presented in the last column of Table 1. Also given in parentheses is the difference between the widths of the high field ($m_N = -1$) and low-field hyperfine peaks, Δ , which is approximately proportional to the rotational correlation time and a function of the known hyperfine and *g*-factor anisotropies of the nitroxide radical.¹⁵

As shown in the spectra in frozen solution,¹² there is a slight trend toward peak broadening as the expected distance between the radical sites decreases. Using published estimates of the anisotropies of the nitroxide group¹⁵ the linewidth differences yield estimates of *ca.* 300 and 800 ps for the rotational correlation times, τ_R , of the monoradical and **1**, respectively. These estimates of τ_R and the viscosity of toluene at 213 K¹⁷ yield values of the Stokes–Einstein–Debye radius of the mononitroxide and isomers of **1** of 4.4 and 5.5–6.0 Å, respectively, which is reasonably close to an estimate of 5 Å for the van der Waals radius of C₆₀.¹⁸ The larger value of the radius of **1** is consistent with the presence of the additional nitroxide “sidearm”.

The estimate of τ_R for **1** may also be used to evaluate the likely contribution to the EPR linewidth due to the dipolar coupling of the electron spins modulated by the rotation of the molecule using a simple model for two identical spins.¹⁹ The estimates range from less than 5% of the observed linewidth for *trans-1* to *ca.* 30% for *e-5*, which is also consistent with the relatively small dipolar contributions to the spectra in frozen solution.¹²

In conclusion, bisadduct isomers of a H₂@C₆₀ derivative with nitroxide addends have been synthesized, isolated and

characterized by a combination of TLC, UV-Vis, ¹H NMR, and EPR spectroscopy. A striking result is the observation that ¹H NMR of endohedral H₂ shows well-separated chemical shifts for the bisadduct isomers. The study has potential applications for assigning structures and identifying purity of the C₆₀ bisadduct isomers.

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