



N-Unsubstituted fulleropyrrolidine derivatives: reinvestigation, structural reassignment and new insight

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ABSTRACT

The reaction of [60]fullerene with α -amino acids and aldehydes affording N-unsubstituted 2,5-disubstituted fulleropyrrolidines was reinvestigated. The previously reported stereochemistry should be reassigned. A reversible interconversion between the *cis* and *trans* stereoisomers of fulleropyrrolidines was observed for the first time.

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1,3-Dipolar cycloaddition reaction is one of the most effective and convenient methods to functionalize fullerenes. Prato and co-workers¹ were the first to establish such 1,3-dipolar cycloaddition protocol by addition of azomethine ylides to [60]fullerene (C_{60}). Then reactions of C_{60} with a series of azomethine ylides generated from various α -amino acid derivatives and different aldehydes, known as Prato reaction, were successfully employed to prepare fulleropyrrolidine derivatives.² Among them, much fewer examples of 2,5-disubstituted fulleropyrrolidines consisting of both *cis* and *trans* isomers have been reported.^{3–5} N-Unsubstituted 2,5-disubstituted fulleropyrrolidines are important precursors for further functionalizations.^{4b,6}

Structure misassignments of fullerene products caused confusion, yet happened occasionally in the literature. For example, the reported [5,6]-closed adducts generated from the reaction of C_{60} with azidoformates⁷ were later reassigned as [5,6]-open adducts,⁸ and the previously reported [6,6]-open adduct⁹ produced from the reaction of C_{60} with a nitrile ylide proved to be a [6,6]-closed adduct.¹⁰

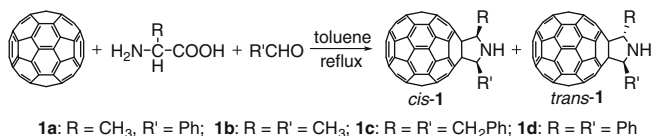
Wilson and co-workers described the reaction of C_{60} with amino acids and aldehydes affording both *cis* and *trans* isomers of N-unsubstituted 2,5-disubstituted fulleropyrrolidines.^{4a} The assignment of the *cis* and *trans* isomers was solely based on the ¹H NMR chemical shifts of the pyrrolidine methine protons. Their criterion was based on the assumption that *the signals for the cis-isomers always appear further downfield than the corresponding*

signals for the trans-isomers.^{4a} This assignment was questioned by Komori et al.¹¹ and was contradictory to the chemical shift trend for the pyrrolidine methine protons of other N-unsubstituted 2,5-disubstituted fulleropyrrolidines.^{3,11} Wilson and co-workers attempted to reclaim their assignment by treating the *cis* and *trans* isomers of fulleropyrrolidines with a chiral isocyanate and resolving the resulting diastereoisomers. However, the demonstrated example consisting of a 1:1 *cis/trans* mixture of 2,5-dimethylfulleropyrrolidine was not appropriate to correlate with the ¹H NMR chemical shifts of the pyrrolidine methine protons.¹² We believe that the *cis* and *trans* isomers can be unequivocally assigned based on their NOESY and ¹³C NMR spectra, which were not measured in Wilson's work.⁴ Another interesting phenomenon in Wilson's work lied in the stereoselectivity: *cis* isomer was the major or even exclusive product in some cases while reversed stereoselectivity was observed in other cases. In order to avoid the confusion caused by misleading structure assignment and to better understand stereoselectivity, herein we reinvestigate a few selected reactions reported in Wilson's work, and correct the misassignments for the *cis* and *trans* isomers of fulleropyrrolidines. Furthermore, we also disclose the intriguing interconversion of the *cis* and *trans* isomers.

The reaction of C_{60} with alanine and benzaldehyde, that with alanine and acetaldehyde, that with phenylalanine and phenylacetaldehyde, and that with phenylglycine and benzaldehyde were chosen for our investigation. The first reaction afforded isomers of unsymmetrical fulleropyrrolidines (*cis*-**1a** and *trans*-**1a**), the latter three gave isomers of symmetrical fulleropyrrolidines (*cis*-**1b** and *trans*-**1b**, *cis*-**1c** and *trans*-**1c**, *cis*-**1d** and *trans*-**1d**, respectively) (Scheme 1).

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Scheme 1. The cycloaddition reaction of C₆₀ with azomethine ylides generated in situ from α -amino acids with aldehydes.

A typical reaction was carried out by treating 72.0 mg of C₆₀ with 2 equiv of an amino acid and 5 equiv of an aldehyde in refluxing toluene for the designated time under a nitrogen atmosphere. After usual workup, the products along with recovered C₆₀ were obtained by flash column chromatography on a silica gel column. It should be pointed out that we successfully achieved the separation of individual cis and trans isomers of both **1b** and **1c** by employing a very long silica gel column.¹³ The reaction times and product yields along with recovered C₆₀ are listed in Table 1.

The cis and trans isomers of **1a**, **1b**, **1c**, and **1d** were unambiguously assigned based on their MS, ¹H NMR, ¹³C NMR, IR, UV–vis, and NOESY spectra.¹⁴ For the unsymmetrical fulleropyrrolidine **1a**, which has a C₁ symmetry, the stereochemistry could not be deduced from the ¹³C NMR spectra, but could be determined by the NOESY spectra. The NOESY spectrum of *trans*-**1a** lacked the cross peak between the two methine protons, but clearly showed the cross peak between either of the methine protons and the methyl protons (Fig. 1), unequivocally proved the assigned structure. For

Table 1

Yields and conditions for the cycloaddition reactions of C₆₀ with azomethine ylides in situ generated from α -amino acids with aldehydes

Entry	R ₁	R ₂	Reaction time (h)	Yield (%)		Recovered C ₆₀
				Cis isomer	Trans isomer	
1	CH ₃	Ph	9	15	19	52
2 ^a	CH ₃	CH ₃	27	5	21	67
3	CH ₂ Ph	CH ₂ Ph	3	6	32	30
4	Ph	Ph	14	32	—	59

^a Repeated separation by column chromatography was required to get pure isomer.

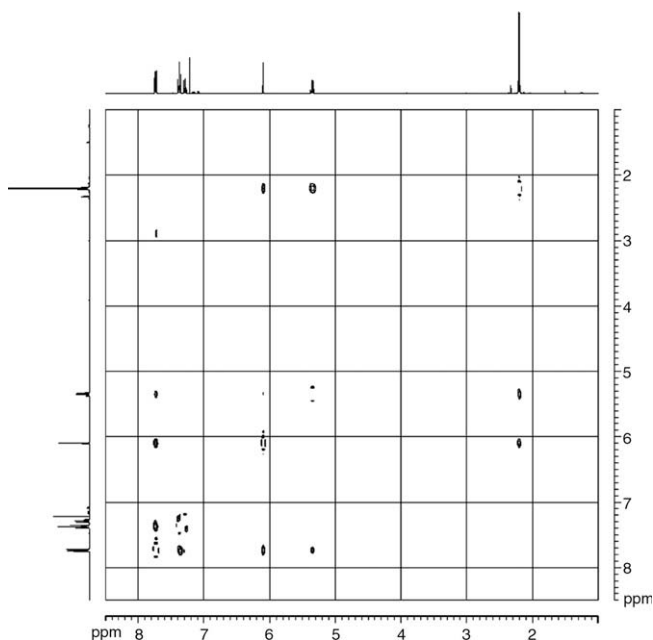


Figure 1. NOESY spectrum of *trans*-**1a**.

Table 2

The ¹H NMR chemical shifts for the methine protons on the pyrrolidine ring of **1a–d**

Entry	Compound	Cis isomer	Trans isomer
1	1a	5.80, 4.96	6.10, 5.35
2	1b	4.80	5.07
3	1c	4.71	5.07
4	1d	5.96	—

symmetrical fulleropyrrolidines **1b–d**, the cis isomers with C_s symmetry should theoretically give 32 peaks including 4 half-intensity ones (corresponding to 1C), while the trans isomers with C₂ symmetry should exhibit 30 peaks with equal intensity. Experimentally, half-intensity peaks were observed only in the ¹³C NMR spectra of cis isomers of fulleropyrrolidines **1b–d**, confirming our assigned stereochemistry.

After the molecular structures including stereochemistries of fulleropyrrolidines **1a–d** had been unequivocally assigned, the ¹H NMR spectra of their cis and trans isomers were compared. The chemical shifts for the pyrrolidine methine protons of fulleropyrrolidines **1a–d** are listed in Table 2. As seen from Table 2, the signals for the cis isomers were shifted upfield by 0.27–0.39 ppm relative to those for the trans isomers. The same phenomenon could also be found in other reported fulleropyrrolidines.^{3,11,15} Therefore, we conclude that Wilson's structure assignments⁴ were incorrect and should be reassigned. The previously assigned cis and trans isomers⁴ should be reassigned as trans and cis isomers, respectively. Accordingly, other structure assignments^{5,6a} based on Wilson's criterion were most likely misassigned.

Another issue that attracted our attention in Wilson's work is the isomeric distribution. The cis isomer was reported to be the major product for **1a** and **1c**,^{4a,16} while a 1:1 cis/trans isomeric mixture was obtained for **1b**.^{4b} However, the trans isomer was the major product for **1a**, **1b**, and **1c** in our case. Through our extensive investigation on these reactions, we found that the main product was heavily dependent on the reaction conditions. As an example, when the reaction of C₆₀ with alanine and benzaldehyde affording **1a** was extended from 9 h to 21 h in toluene at 110 °C, the major product was changed to the cis isomer. The yields for the *cis*-**1a** and *trans*-**1a** isomers were 28% and 15%, respectively. We surmised that this unusual behavior might result from the conversion between the *trans*-**1a** and *cis*-**1a** isomers. To confirm our hypothesis, pure *cis*-**1a** (10 mg) and *trans*-**1a** (10 mg) were separately dissolved in toluene (15 mL) and heated to 110 °C for 24 h under a nitrogen atmosphere. Unexpectedly, the same isomeric ratio (cis/trans = 71:29) was observed for both isomers. Obviously, the interconversion between *trans*-**1a** and *cis*-**1a** isomers existed an equilibration in refluxing toluene. It is noteworthy that *trans*-**1a** could be converted to *cis*-**1a** even at room temperature. Stirring *trans*-**1a** (10.0 mg) at ambient temperature in 1 mL of carbon disulfide/dimethyl sulfoxide (v/v, 5:1) for 24 h led to a mixture with a cis/trans ratio of 57:43. Unlike product **1a**, the conversion of **1b** and **1c** was very sluggish in refluxing toluene. To accelerate the conversion *o*-dichlorobenzene (ODCB) was employed as the solvent and the reaction temperature was elevated. Multi-adducts of C₆₀ were obtained when the cycloaddition reaction was conducted with longer reaction time in refluxing toluene or ODCB. Therefore, the isomeric mixture of **1b** and **1c** was first separated from the reaction mixture and then heated in refluxing ODCB. Fulleropyrrolidine **1b** with a cis/trans ratio of 21:79 was heated in refluxing ODCB for 12 h and gave an obvious change of the cis/trans ratio to 85:15; Similar procedure was carried out for adduct **1c** and gave the analogous change of the cis/trans ratio from 14:86 to 73:27 (Fig. 2). This observation showed that the trans isomer was the major product for the cycloaddition reaction affording **1a–c** in refluxing toluene with short-reaction time, but the cis iso-

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