Pergamon

Tetrahedron Letters 39 (1998) 4187–4190

TETRAHEDRON
LETTERS

Resolution and Absolute Configuration of a C_2-Symmetric *Trans* -2,5-Disubstituted Fulleropyrrolidine

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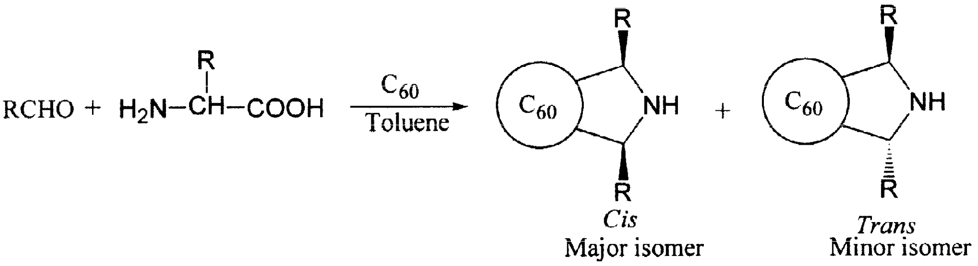
Received 2 February 1998; accepted 30 March 1998

Abstract. A series of 2,5-disubstituted fulleropyrrolidines have been prepared by reaction of C_{60} with amino acids and aldehydes. The *trans*-d,l isomers could be resolved using a chiral isocyanate to prepare diastereomeric urea derivatives. The absolute configuration of the C_2-symmetric *trans* isomers was assigned by correlation of their CD spectra with our previously reported sector rule for chiral fullerene monoderivatives. © 1998 Elsevier Science Ltd. All rights reserved.

Among the numerous methods for functionalizing fullerenes, 1,3-dipolar cycloadditions have been extensively applied. In particular, the reaction of azomethine ylide with C_{60} results in the formation of heterocyclic derivatives called fulleropyrrolidines.[1] *N*-unsubstituted fulleropyrrolidines can be further derivativitized at nitrogen to provide new useful materials. We have recently reported new methodologies for preparing such compounds from the reaction of C_{60} with 1,3-dipoles derived from amino acids and aldehydes.[2] While other groups have reported alternative routes to such compounds,[3] an advantage of our approach is that a wide variety of 2,5-disubstituted fulleropyrrolidines can be easily prepared from readily available starting materials (Equation 1). The 2,5-disubstituted fulleropyrrolidines are usually formed as mixtures of *cis* and *trans* isomers. Yields and product ratios are collected in Table 1.



Cis
Major isomer

Trans
Minor isomer

[1]

In our initial report on this reaction, we proposed that the major isomer appeared to be the *cis* isomer, based on known ylide stereoselectivity.[4] The *trans* azomethine ylide (which leads to the *cis* product) is more stable for steric reasons than the *cis* azomethine ylide (which leads to the *trans* product).[2] After our paper appeared, another report questioned our structure assignment and suggested that the major isomer was the *trans* isomer.[5] Our tentative structure assignment [2] is now unequivocally confirmed by the series of experiments described below.

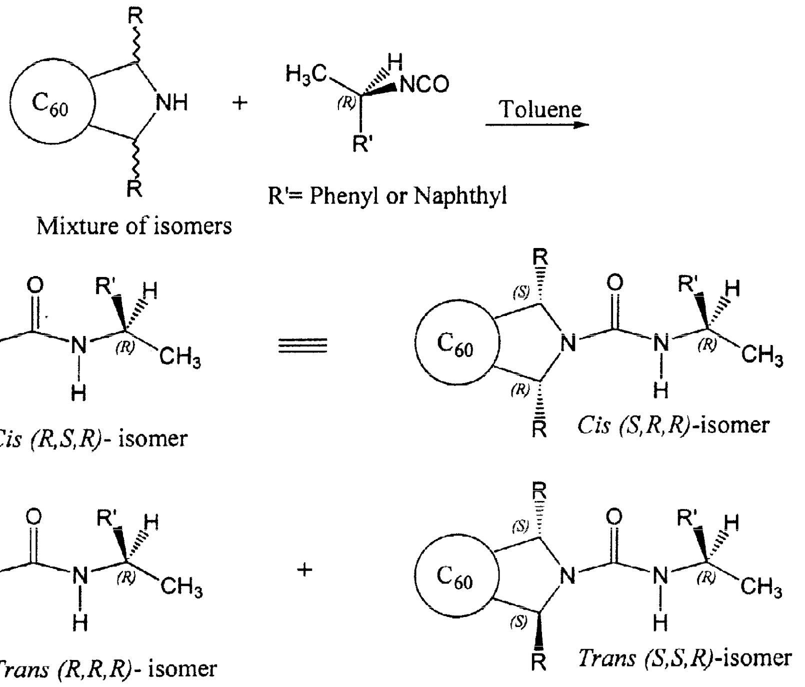
The nucleophilicity of the nitrogen atom in a fulleropyrrolidine is less than that of a typical pyrrolidine,[6] and steric hindrance due to substitution at the 2,5-positions also contributes to lower reactivity of fulleropyrrolidines. Nonetheless, we have found that isocyanate derivatives react smoothly with many fulleropyrrolidines to form urea derivatives.[7] Since chiral isocyanates are excellent resolving reagents and are commercially available, we have used these materials for enantiomeric resolution of chiral fulleropyrrolidines.

PII: S0040-4039(98)00781-3

Table 1. Product yields and Buckyclutcher HPLC retention data for Cis / Trans compounds from Equation 1

Entry	R	Yield[a] HPLC (R.T.)[b] *Trans / Cis*	^{1}H-NMR (2:1CS_2/$CDCl_3$)
1	CH_3	20% 5.5/7.4	*trans:* 4.84-4.90 (q, *J*=6.59Hz, 1H), 1.30 (d, *J*=7 Hz, 6H) *cis:* 5.11-5.18 (q, *J*= 6.79Hz, 1H), 2.08 (d, *J*=7 Hz, 6H)
2	$CH(CH_3)_2$	23% 11.2[c]	*trans:* 4.51-4.53 (d, *J*= 6.3Hz, 2H), 3.65-3.75 (m, 4H), 1.40-1.69 (m, 12H) *cis:* 4.54-4.57 (d, *J*=6.24Hz, 2H), 3.41-3.53 (m, 4H), 1.40-1.69 (m, 12H)
3	$CH_2CH(CH_3)_2$	15% 13.8/20.2	*trans:* 4.92-4.94 (d, *J*=4.2Hz, 2H), 2.21-2.39 (m, 6H), 1.23-1.24 (d, *J*=6.20Hz, 6H) *cis:* 4.97-4.99 (d, *J*=4.1Hz, 2H) 2.21-2.39 (m, 6H) 1.21-1.22 (d, *J*=6.23Hz, 6H)
4	Ph	35%[d]	*cis:* 8.06-8.02 (m, 4H), 7.51-7.35 (m, 6H), 6.04 (s, 2H)
5	CH_2Ph	28% 13.0/17.6	*trans:* 7.66-7.10 (m, 10H), 4.80 (dd, J_1=3.1Hz, J_2=10.5Hz, 2H), 3.93 (dd, J_1=3.1Hz, J_2=13.5Hz, 2H), 3.38 (dd, J_1=10.5Hz, J_2=13.5Hz, 2H) *cis:* 7.66-7.10 (m, 10H), 5.17 (dd, J_1=3.6Hz, J_2=10.8Hz, 2H), 3.74 (dd, J_1=3.6Hz, J_2=13.4Hz, 2H), 3.54 (dd, J_1=11.1Hz, J_2=13.5Hz, 2H)

(a). Isolated yields. (b). Eluent: 1:1 toluene / hexane. (c). Only one peak is observed for both *cis* and *trans* isomers. (d). Only the *cis* isomer was formed.



[2]

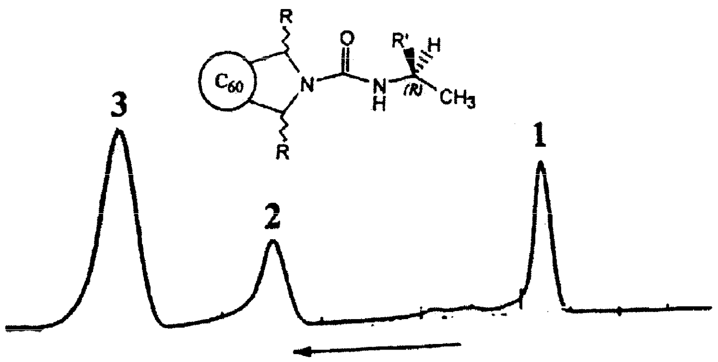


Figure 1. Silica HPLC for diastereomeric urea mixture from *cis/trans*-2,5-dimethylfulleropyrrolidine and *R*-(+)-(1-naphthyl)-ethyl-isocyanate.

We illustrate the resolution using *cis*/*trans*-2,5-dimethylfulleropyrrolidines. Reaction of *R*-(+)-(1-naphthyl)-ethyl isocyanate (Aldrich Chemical Co.) with an approximately 1:1 mixture of *cis/trans*-1,3-dimethylfulleropyrrolidine (prepared by the reaction of C_{60} with acetaldehyde and alanine) gave a urea product whose HPLC chromatogram shows three peaks for the expected *cis* (meso) and *trans* (d,l)-isomeric ureas (Figure 1.) The first two peaks correspond to an equimolar ratio of ureas from the *trans* (d,l) isomers and the third peak corresponds to the urea derived from the *cis* (meso) isomer in a ratio of 1:1:2. The three peaks were collected and spectral data showed that each was a pure compound. Circular dichroism (CD) spectra were obtained for all three diastereomers. There was no significant CD in the 350-500 nm range for Peak 3 as expected for the *cis* (meso) compound. On the other hand, Peaks 1 and 2 (the *trans* (d,l) ureas) showed almost mirror image CD's (Figure 2) with significant (+) and (-) Cotton effects in the region of 430 nm (peak 1 has a positive Cotton effect at 430 nm and peak 2 has a negative Cotton effect at 430 nm.). The 430 nm region is the position of a characteristic UV band recognized as a fingerprint for mono-adducted fullerenes at a 6,6-double bond.[8]

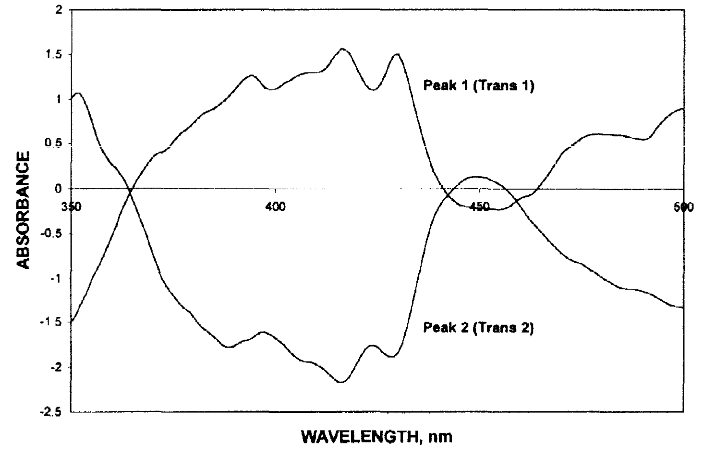


Figure 2. CD Spectra of *R*-(+)-(1-naphthyl)-ethyl-trans-2,5-dimethylfulleropyrrolidine urea derivatives corespoinding to HPLC peaks 1 and 2 (cf. Figure 1.)

We have previously proposed [8] that chiral fullerene derivatives can be divided into two categories. The first type are compounds where the chirality originates from an intrinsically chiral fullerene chromophore, first identified by Hawkins.[9] The second type of compound has a chiral group attached to a symmetric fullerene core at a 6,6-bond. The appended chiral group can perturb the fullerene chromophore and lead to an induced CD effect, known as a Cotton effect. We have demonstrated the use of such effects for *a priori* determination of absolute configuration of such adducts, and have proposed a sector rule for the assignment of the absolute configuration of groups attached to the fullerene core (Figure 3A). [8] Thus, by examination of a sector projection of a fullerene compound, one can predict the absolute configuration of the compound based on the sign of the Cotton effect at 430 nm.

This sector rule was applied to the *trans*-2,5-dimethyl fulleropyrrolidine isomers. The absolute configuration of the *trans* I isomer (Figure 2) was assigned as (*R*,*R*) and the *trans* II isomer as (*S*,*S*).This assignment is obtained by comparing the position of atoms in the appropriate sectors with the structures of *trans* I (methyl in the top left or bottom right (+) sectors, see Figure 3B) and *trans* II (methyl in the top right or bottom left (-) sectors). This sector rule analysis has been correlated with fullerene derivatives of known absolute configuration, and is consistent with results obtained by other groups.[10] We expect that the use of the fullerene sector rule for absolute configuration prediction will be a powerful tool in basic chiral chemistry studies.

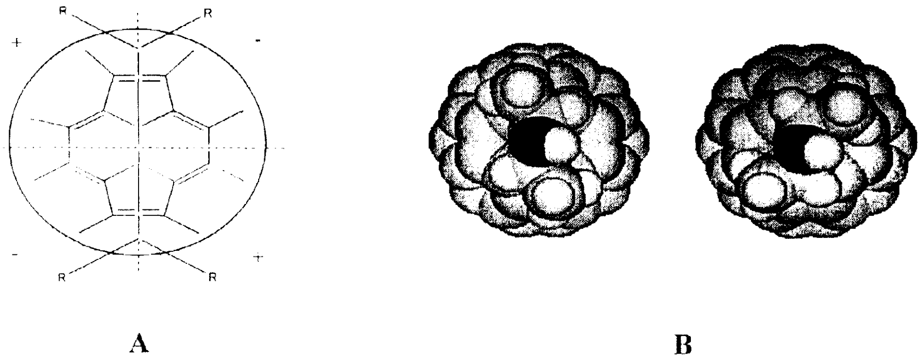


Figure 3. **A**. Sector Rule for C_{60} Derivatives. The vertical axis is drawn through the 6,6 bond. Location of atoms in (+) or (-) sectors defines the sign of the Cotton effect at 430 nm, which can be used to determine the absolute configuration of attached groups. **B.** Computed model of 2,5-dimethylfulleropyrrolidine isomers *R,R-trans*-I and *S,S-trans*-II. The urea group has been removed for clarity

Acknowledgment. We thank the NSF (CHE-9400666) and the NYU Research Challenge Fund for partial support of this work.

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