

## Unambiguous and Rapid *cis/trans* Assignment of Aryl-carboxy Disubstituted Cyclopropanes Using NMR.

Arlette Solladié-Cavallo\* and Thomas Isarno

Laboratoire de Stéréochimie Organométallique associé au CNRS, ECPM/Université L.Pasteur, 1 rue B. Pascal, 67008-Strasbourg.  
ascava@chimie.u-strasbg.fr

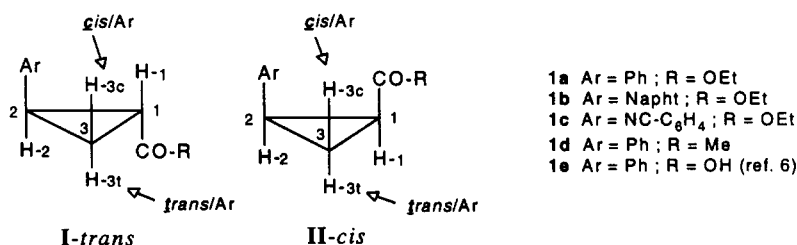
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**Abstract :** It is shown that *cis* or *trans* structures of aryl-carboxy disubstituted cyclopropanes can be directly, rapidly and easily determined by  $^1\text{H}$  NMR with no need of comparing both *cis* and *trans* isomers when vicinal coupling constants are in the range of 8–9 Hz (*cis*-isomer) or 4–6 Hz (*trans*-isomer). More, when the precision of the  $^1\text{H}$  NMR is  $\pm 0.5\text{Hz}$  (the usual conditions), the most deshielded signal is a 'ddd' for the *trans* isomer and a 'q' (quadruplet) for the *cis* isomer. © 1999 Elsevier Science Ltd. All rights reserved.

Polysubstituted cyclopropanes have been extensively studied since the first Simmons-Smith synthesis in 1958.<sup>1</sup> However, during work on enantioselective synthesis of disubstituted aryl-carboxy cyclopropanes<sup>2</sup> **1a-d**, Figure 1, we have been confronted with the difficulty of finding in the literature any examples of NMR determinations of the *cis* and/or *trans* structure of this kind of compound although they had already been synthesized by other methods.<sup>3–6</sup> *Cis/trans* ratios are given without indication of the methods used for the assignment of the structures while the determination of absolute configuration is always described.<sup>7</sup>

We report here a complete study of  $^1\text{H}$  and  $^{13}\text{C}$  NMR features (chemical shifts, coupling constants and patterns) of these type of cyclopropanes **1** which demonstrate that NMR is a rapid and unambiguous method for *cis/trans* assignment.

Figure 1



The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data are gathered on Tables 1, 2 and 3.

In cyclopropanes **1a**, **1b**, and **1c** the chemical shifts of the ethyl groups are shielded in isomers **II** compared to isomers **I**: the CH<sub>2</sub>-quadruplets and the CH<sub>3</sub>-triplets are shielded by about 0.2–0.35ppm (Table 1 columns 7 and 8, compare lines 1 and 2, 3 and 4, 5 and 6). In the same way the CH<sub>3</sub>-singlet in cyclopropane **1d** is shielded by 0.28ppm in isomer **II** compared to isomer **I**.

These shieldings suggest that the ethyl-groups and the methyl are *cis* to the aromatic-groups in isomers **II**

and therefore the *cis*-structure can be assigned to these isomers : **II** = *cis*. However assignment on the basis of chemical shifts needs both isomers for comparison. A complete analysis of the  $^1\text{H}$  NMR spectra and determination of the vicinal-coupling constants, which could, in principle, be used directly for *trans/cis* assignment, was undertaken.

In cyclopropane **1a-I**-(*trans*) the most deshielded ddd (at 2.51 ppm, Table 1) was assigned to H-2 ( $\text{CH-Ph}$ ) on the basis of the absence of this multiplet in the corresponding 2-deuterated cyclopropane which was prepared from the corresponding deuterated sulfonium salt.<sup>8</sup> This result is in accord with literature results concerning non deuterated and 2,3-dideuterated cyclopropane **1e**.<sup>9</sup> Therefore the most deshielded multiplets (at 2.69, 2.54, 2.53 ppm, Table 1, column 3) were also assigned to the H-2 ( $\text{CH-Ar}$ ) in, respectively, **1b-I**-(*trans*), **1c-I**-(*trans*) and **1d-I**-(*trans*).

If one examines the  $^1\text{H}$  NMR spectra and compare isomers **I**-(*trans*) and **II**-(*cis*) of all cyclopropanes, the most obvious change in pattern is the 'quadruplet' aspect of the most deshielded signal for isomers **II**-(*cis*) in all cases (Table 1, column 3 and Figure 2). Because, in cyclopropane **1e-cis**<sup>9</sup> the most deshielded signal (at ~2.6ppm) has been also shown to be due to H-2 ( $\text{CH-Ph}$ ), the most deshielded signals (quadruplets at 2.59, 2.74, 2.58 and 2.70ppm, Table 1, column 3) of all the **II**-(*cis*) isomers in cyclopropanes **1a-1d** were assigned to proton H-2.

Assignments of the other ddd to H-1 and to the  $\text{CH}_2$  in position 3, were done through  $^1\text{H}$ - $^{13}\text{C}$ -correlation experiments.

Interpretation of the four multiplets, Figure 2, corresponding to the cyclopropyl protons, extraction of all the coupling constants and assignment of H-3c and of H-3t were then straightforward.

It appeared (Table 2) that, in all cases, the values of the coupling constants between H-1 and H-2 are significantly smaller in isomers **I**,  $^3J_{1,2} = 4$  Hz, than in isomers **II**,  $^3J_{1,2} = 9$  Hz. This is in accord with the previous assignment (from chemical shifts) of the *cis* structure to isomers **II**, with known results<sup>10</sup> and with the Karplus-Conroy curves ;  $J$  values corresponding to dihedral angles close to  $0^\circ$  are larger than those corresponding to diedral angles of  $120^\circ$ .

It can thus be concluded from the values of  $^3J_{1,2}$ , which are significantly different in all cases, that isomers **I** are *trans* while isomers **II** are *cis*.

It is worth noting (Table 2, column 7) that while the values of the *cis*-coupling constants between H-2 and H-3t (8.5 to 9 Hz) are identical or close to the values found for H-1/H-2 (9 Hz), the values of the *trans*-coupling constants between H-2 and H-3c are larger (6 to 7.5 Hz, compared to 4 Hz). More the differences ( $^3J_{23t} - ^3J_{23c}$ ) are smaller in the *cis*-isomers ( $\Delta J \sim 1$  Hz) which is responsible (the spectra's resolution being 0.3Hz/pt) for the quadruplet aspect of the signal of H-2 in these *cis*-isomers.

The values of the *cis*-coupling constants linking H-1 and H-3 are smaller (7 to 8.5 Hz) than those found for H-1/H-2 (9 Hz) and the values of the *trans*-coupling constants larger (5 to 5.5 Hz compared to 4 Hz).

However, apart for cyclopropane **1d** where  $J_{13c,cis} = 7$  Hz and  $J_{23c,trans} = 7.5$  Hz, the values of the *cis*-coupling constants (9 - 7.5 Hz) are larger than the values of the *trans*-coupling constants (7.5-4 Hz).

Most interesting is the ~6 ppm shielding of carbon-3 on passing from the *trans*-isomer to the *cis*-isomer (Table 3, column 5) while the shielding of carbon-1, carbon-2 and other carbons are very small, if not nil (Table 3).

**Table 1 :**  $^1\text{H}$  NMR of compounds **1a-1d** ( $\delta$  in ppm,  $\text{CDCl}_3/\text{TMS}$ )

Compd	isomer	Cyclopropyl protons				R group	
		H-2	H-1	H-3c	H-3t		
<b>1a</b>	<b>I-trans</b>	2.51 ddd	1.90 ddd	1.32 ddd	1.61 ddd	4.17 q	1.28 t
<b>1a</b>	<b>II-cis</b>	2.59 ~q	2.09 ddd	1.71 ddd	1.32 ddd	3.85 q	0.95 t
<b>1b</b>	<b>I-trans</b>	2.69 ddd	2.00 ddd	1.43 ddd	1.67 ddd	4.21 q	1.30 t
<b>1b</b>	<b>II-cis</b>	2.74 ~q	2.17 ddd	1.86 ddd	1.42 ddd	3.87 q	0.95 t
<b>1c</b>	<b>I-trans</b>	2.54 ddd	1.95 ddd	1.33 ddd	1.68 ddd	4.18 q	1.20 t
<b>1c</b>	<b>II-cis</b>	2.58 ~q	2.15 ddd	1.71 ddd	1.40 ddd	3.87 q	1.00 t
<b>1d</b>	<b>I-trans</b>	2.53 ddd	2.23 ddd	1.39 ddd	1.69 ddd	2.30 s	
<b>1d</b>	<b>II-cis</b>	2.70 ~q	2.42 ddd	1.82 ddd	1.30 ddd	2.02 s	

**Table 2 :** Coupling constants (in Hz) within the cyclopropyl ring for **1a-1d** \*

Compd	isomer	$J_{12}$	$J_{13c}$	$J_{13t}$	$J_{23c}$	$J_{23t}$	$J_{\text{gem}}$
<b>1a</b>	<b>I-trans</b>	4 (t)	8.5 (c)	5 (t)	6.5 (t)	9 (c)	4
<b>1a</b>	<b>II-cis</b>	9 (c)	5.5 (t)	8 (c)	7.5 (t)	8.5 (c)	5
<b>1b</b>	<b>I-trans</b>	4 (t)	8.5 (c)	5 (t)	6.5 (t)	9.5 (c)	4
<b>1b</b>	<b>II-cis</b>	9 (c)	5.5 (t)	8 (c)	7.5 (t)	8.5 (c)	5
<b>1c</b>	<b>I-trans</b>	4 (t)	8.5 (c)	5 (t)	6 (t)	9 (c)	4
<b>1c</b>	<b>II-cis</b>	9 (c)	5.5 (t)	8 (c)	7.5 (t)	8.5 (c)	5.5
<b>1d</b>	<b>I-trans</b>	4 (t)	8 (c)	5 (t)	6.5 (t)	9 (c)	4
<b>1d</b>	<b>II-cis</b>	9 (c)	5.5 (t)	7 (c)	7.5 (t)	8.5 (c)	5

\* (c) and (t) after the  $J$  values mean that the corresponding  $J$  is *cis* and *trans* respectively.

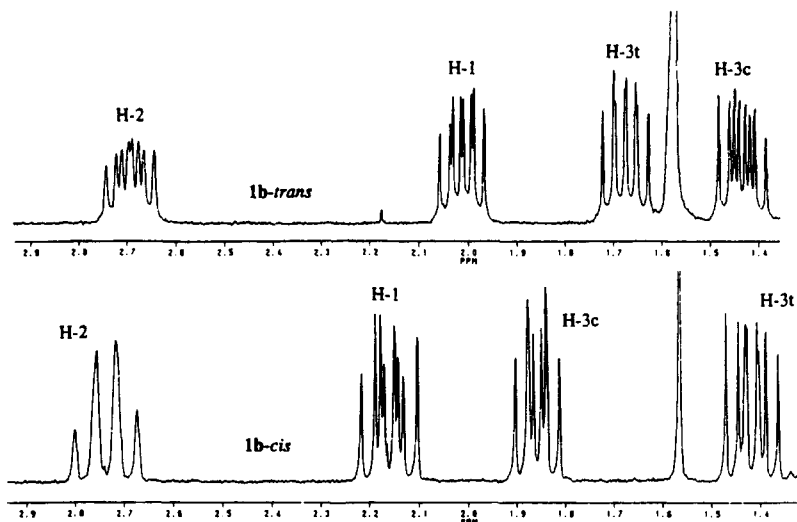
**Table 3 :**  $^{13}\text{C}$  NMR of compounds **1a-1d** ( $\delta$  in ppm,  $\text{CDCl}_3/\text{TMS}$ )

Compd	Isomer	cyclopropyl ring			R group	
		C-1	C-2	C-3		
<b>1a</b>	<b>I-trans</b>	23.5	26.0	17.0	61.0	14.5
<b>1a</b>	<b>II-cis</b>	21.9	25.5	11.2	60.2	14.1
<b>1b</b>	<b>I-trans</b>	24.3	26.5	17.1	60.7	14.4
<b>1b</b>	<b>II-cis</b>	22.2	25.8	11.5	60.3	14.2
<b>1c</b>	<b>I-trans</b>	24.9	25.8	17.6	60.8	14.2
<b>1c</b>	<b>II-cis</b>	22.4	25.4	11.6	60.6	14.2
<b>1d</b>	<b>I-trans</b>	28.4	32.0	19.0	30.0	
<b>1d</b>	<b>II-cis</b>	28.0	31.3	11.7	30.4	

Therefore values in the range 8-9 Hz (4-6 Hz) are directly indicative of a *cis*-relationship (*trans*-relationship), while, of course, for intermediate values (6.5-7.5 Hz) both isomers and comparison will be necessary for a *trans/cis* assignment.

More, for *trans*-isomers the most deshielded signal (corresponding to H-2) is a 'ddd' while it is a 'q' (quadruplet) for the *cis*-isomers.

Figure 2



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