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Determination of absolute configuration of trans-2-arylcyclohexanols using remarkable aryl-induced ¹H NMR shifts in diastereomeric derivatives

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Abstract—A facile determination of the absolute configuration of *trans*-2-arylcyclohexanols was achieved. It takes advantage of the observations of the remarkable aryl-induced ¹H NMR shifts that seems to be ascribable to the discrimination of the diastereo-environment between intermediary optically active diastereomers by intramolecular CH/ π interaction. © 2001 Elsevier Science Ltd. All rights reserved.

As for the method for the isolation of optically active secondary alcohols, optical resolution using chiral auxiliary has been well used.¹ It is, however, generally difficult to predict the absolute stereochemistry of the resolved alcohols.² Therefore X-ray crystallographic analysis or ¹H NMR spectroscopic analysis such as the modified Mosher's method³ is used to determine the absolute configuration. Although X-ray crystallographic analysis is quite useful to determine the absolute configuration, it is required to obtain good quality single crystals of the target molecule, which is sometimes difficult. To apply the ¹H NMR spectroscopic analysis such as the modified Mosher's method, though with some exception,⁴ both of the corresponding diastereomeric esters⁵ with α-methoxy-α-trifluoromethylphenylacetic acid are required. We now present a new methodology for the determination of absolute configuration of trans-2-arylcyclohexanols using ¹H NMR spectroscopic analysis based on a discrimination of the diastereo-environment due to an intramolecular CH/ π interaction.⁶ The interaction is a non-bonding interaction⁶ between the C-H bond and the π system, that was first proposed by Nishio and co-workers.7

First we performed the ¹H NMR analysis of *trans*-2arylcyclohexanol esters **3** and **4** both bearing a CH moiety, derived from optically active 3β -acetoxy- Δ^5 -etiocholenic acid chloride (2),⁸ and a π moiety derived from (±)-*trans*-2-arylcyclohexanols (1)⁹ in the same molecule (see the structure in Table 1). In this system, we postulate that an effective intramolecular CH/ π interaction between the aromatic ring moiety of the racemic alcohols and the β -methyl moiety at the 18position (C18-CH₃) of the optically active steroid ring exists only in the (1*S*,2*R*)-isomer **3a**.¹⁰ The molecular orbital analysis of the compounds, **3a** and **4a**,¹¹ suggested this possibility, as shown in Fig. 1.¹¹

With the above data in mind, a mixture of two diastereomeric esters 3a and 4a from (±)-trans-2phenylcyclohexanol was prepared. The ¹H NMR spectrum of the mixture indicated that the chemical shift (δ (0.039) of the C18-CH₃ of one isomer is guite different from that (δ 0.449) of the other isomer, suggesting that the two methyl groups are placed in quite different environments. To determine which isomer shows the remarkable high field shift, stereo-defined 3a was prepared from enantiomerically pure (1S,2R)-1a. Consistent with the prediction from MO calculations, the C18-CH₃ appeared at unusually high field in the 1 H NMR spectrum (Table 1, entry 1). In addition, 3a showed red shift of E_1 absorption than 4a in UV spectrum in acetonitrile (λ_{max} : 192 nm; λ_{max} : 187 nm, respectively).¹² It is therefore reasonable to consider that the unusual high field shift (δ 0.039) is derived from an affinity such as the CH/ π interaction.¹³ More clear-cut evidence for the interaction was obtained by the X-ray crystallographic analysis of (1S, 2R)-isomer

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Entry	Ar	Chemical shift of protons on C18-Me in 3 or 4 $[\delta \text{ (ppm)}]^a$		Predicted configuration of resolved 1	Actual configuration of resolved 1	Isolated yield of resolved 1 (%) ^b
1	Ph	3a	0.039	_	$(1S,2R)^{c}$	_
		4a	0.449	_	$(1R, 2S)^{c}$	_
2	p-Methoxyphenyl	3b ^d	0.006	$(1S^*, 2R^*)$	$(1S,2R)^{\rm e}$	14
		4b ^d	0.490	$(1R^*, 2S^*)$	(1R, 2S)	9
3	2-Naphthyl	3c ^d	-0.246	$(1S^*, 2R^*)$	$(1S,2R)^{e}$	27
		$4c^{d}$	0.426	$(1R^*, 2S^*)$	(1R, 2S)	5 ^f
4	<i>p</i> -Tolyl	3d	0.068	$(1S^*, 2R^*)$	_	_
		4d	0.481	$(1R^*, 2S^*)$	_	_
5	p-Chlorophenyl	3e	0.116	$(1S^*, 2R^*)$	_	_
		4 e	0.486	$(1R^*, 2S^*)$	_	_
6	1-Naphthyl	3f	-0.214	$(1S^*, 2R^*)$	_	_
	-	4f	0.322	(1 <i>R</i> *,2 <i>S</i> *)	_	_

^a In CDCl₃ at 25°C.

^b Isolated yield of resolved 1 was based on a racemic 1.

^c A commercially available substrate with known absolute configuration was used.

^d Diastereomeric isomer was separated by recrystallization.

^e Absolute configuration was determined by X-ray crystallographic analysis of the corresponding 3.

^f Optical purity was 65% ee due to the difficulty in separation of the corresponding diastereomers.



Figure 1. Calculated conformation of (1S,2R)-isomer 3a showing CH/ π interaction.

3b (see Fig. 2).^{5e,14} C18-CH₃ was found to be placed in close proximity to the π -face of the anisyl group. The shortest inter-atomic distance between the CH moiety and the aromatic π plane was shorter (2.92 Å) than the sum of each van der Waals radius.¹⁵ The NOESY spectrum also supported the close proximity between the CH moiety and the π moiety.¹⁶ Hence, it can be seen that the structure in crystals is also retained in solution as the major conformation. On the other hand, X-ray crystallographic analysis of compound **4b** derived from (1*R*,2*S*)-alcohol showed the absence of a similar interaction in this molecule (Fig. 3).

These findings led us to assume that the molecule,

which shows remarkable shielding effect to the neighborhood of TMS peak in the ¹H NMR spectrum, must always have (1S,2R) configuration. This is because the interaction seems to require a highly ordered conformation. Certainly compound **3c**, which showed remarkable shielding effect in ¹H NMR, also has (1S,2R) configuration (Table 1, entry 3).

Thus, the prediction of the configuration using ¹H NMR shifts seems to hold for various aryl cyclohexanols. More examples of chiral recognitions are shown (Table 1, entries 4–6). It was found that this methodology could be applied to various aryl functions. Besides, it is worth noting that the LAH reduction of the individual diastereomer (**3** or **4**) gave the corresponding optically pure alcohol^{17,18} in almost quantitative yield (Table 1, entries 2, 3). We assume that the stereoelectronic effect and/or the rigidity of the configuration induced by the adjacent carbonyl group exerts such a stout CH/ π interaction in the ester **3** (Fig. 4).

In conclusion, we have discovered that an intramolecular CH/π interaction can discriminate the diastereoenvironment between optically active diastereomers in the crystal structure. This makes it possible to determine the absolute configuration of various *trans*-2-aryl-



Figure 2. ORTEP drawing of (1S, 2R)-isomer 3b.



Figure 3. ORTEP drawing of (1R,2S)-isomer 4b.



Figure 4. Speculation: contribution of the stereoelectronic effect.

cyclohexanols by ¹H NMR analysis. In addition, the methodology developed in this study would also be applicable to the ¹H NMR spectroscopic measurement of the optical purity of various *trans-2*-arylcyclohexanols.

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