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A novel determination method of the absolute configuration of 1-aryl-1-alkylalcohols and amines by an intramolecular CH/π shielding effect in ^{1}H NMR

Masato Matsugi,[a] Kinuyo Itoh,[a] Masatomo Nojima,[a] Yuri Hagimoto[b] and Yasuyuki Kita[b,*]

[a]*Department of Materials Chemistry, Graduate School of Engineering, Osaka University, 2-1, Yamada-oka, Suita, Osaka 565-0871, Japan*

[b]*Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565-0871, Japan*

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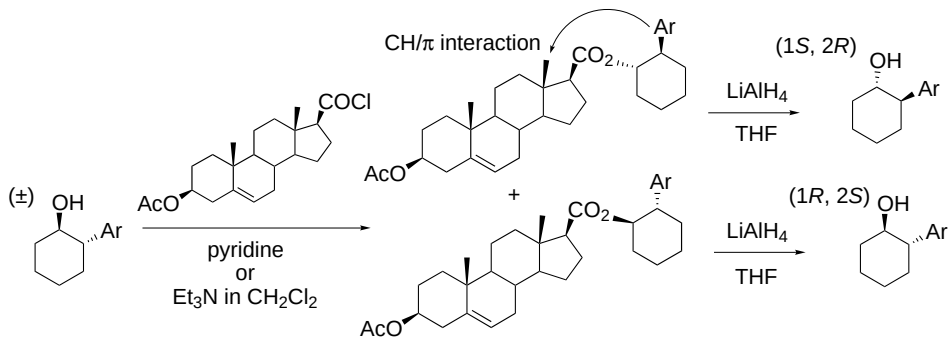
Abstract—A novel method for determination of the absolute configuration of various 1-aryl-1-alkylalcohols and amines was achieved by the observation of an intramolecular CH/π shielding effect in ^{1}H NMR. (*S*)-Isomer of the diastereomers always shows effective shielding effect.

We have already reported that the intramolecular CH/π interaction[1] can discriminate the diastereo-environment in some optically active molecules.[2]

One of the main reasons for the effective diastereo-recognition seems to be the rigid conformation of the 2-arylcyclohexanol moiety. However, we have found that the remarkable ^{1}H NMR shifts were observed in more loosely arranged acyclic arylalcohols. Here we show a method of determination of the absolute configuration[3] of various 1-aryl-1-alkylalcohols and amines by an intramolecular CH/π shielding effect in ^{1}H NMR.

The diastereomers (**3** and **4**) were easily obtained from the reaction of various (±)-1-aryl-1-alkylalcohlols **1** and 3β-acetoxyetienic acid chloride **2**.[4,†] Interestingly, the chemical shift values in ^{1}H NMR of the β-Me at 18 position (C18-CH_3)[5] on the steroid ring were apparently different for the diastereomers (Table 1, entries 2–8). One always appeared near δ 0.5 ppm while the other always appeared near δ 0.7 ppm. We then used compound **1a** having known absolute configuration[6] to clarify which diastereomer shows the shielding effect by the aromatic ring (Table 1, entry 1). As a result, we found that the diastereomer showing the shielding effect was derived from (*S*)-alcohol. It is noteworthy



* Corresponding author. E-mail: kita@phs.osaka-u.ac.jp

† Typical procedure for esterification: To a stirred solution of **2** (420 mg, 1.1 mmol) in CH_2Cl_2 (16 ml) was added **1a** (120 mg, 0.98 mmol) and Et_3N (0.4 ml, 2.9 mmol) at 25°C and stirred for 25 h. After filtration of the white precipitate, the filtrate was washed with water, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/AcOEt, 4:1) to give a mixture of **3a** and **4a** (290 mg, 64%) as white crystals.

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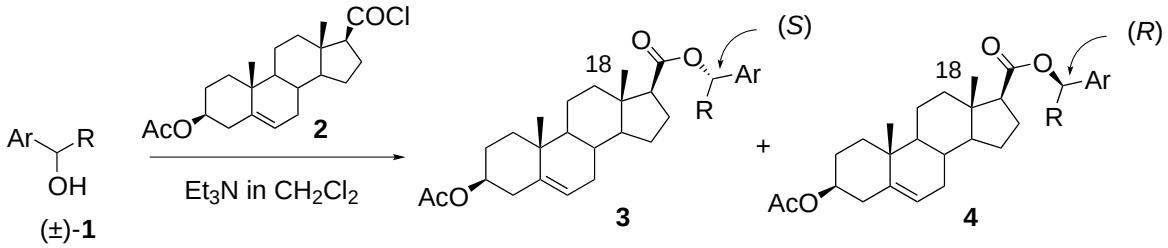
Table 1. ^{1}H NMR spectroscopic determination of the absolute configuration of 1-arylalcohols using CH/π shielding effect



Entry	Ar	R	Chemical shift of protons on C18–CH_3 in **3** or **4** [δ (ppm)][a]	Predicted configuration of resolved **1**	Yield (%)[b]
1	Ph	Me: **3a**	0.51	*S*[c]	64
	Ph	Me: **4a**	0.71	*R*	
2	*p*-Tolyl	Me: **3b**	0.52	*S**	74
	p-Tolyl	Me: **4b**	0.71	*R**	
3	4-Methoxyphenyl	Me: **3c**	0.49	*S**	77
	4-Methoxyphenyl	Me: **4c**	0.70	*R**	
4	4-Chlorophenyl	Me: **3d**	0.51	*S**	66
	4-Chlorophenyl	Me: **4d**	0.70	*R**	
5	2-Naphthyl	Me: **3e**	0.52	*S**	59
	2-Naphthyl	Me: **4e**	0.71	*R**	
6	Ph	Et: **3f**	0.48	*S**	33
	Ph	Et: **4f**	0.71	*R**	
7	2-Pyridyl	Me: **3g**	0.59	*S**	90
	2-Pyridyl	Me: **4g**	0.73	*R**	
8	Bn	Me: **3h**	0.48	*S**	81
	Bn	Me: **4h**	0.63	*R**	

[a] 25°C in $CDCl_3$.
[b] Isolated yields of a mixture of diastereomers by column chromatography.
[c] The configuration was confirmed by use of an enantiomerically pure substrate with known absolute configuration.

that there are almost no aberrations regarding the chemical shift values in the case of 1-aryl-1-alkylalcohols in spite of the use of various kinds of the aromatic moieties (Table 1, entries 1–6). This suggests that this methodology would be highly general for the determination of the absolute configuration of various analogues. In addition, a similar high field shift is also observed in the case of pyridylalcohol (Table 1, entry 7) and homoaryl-type alcohol such as 1-phenylpropan-2-ol (Table 1, entry 8).

Similarly, it is likely that the absolute configuration of 1-aryl-1-alkylamines could be determined easily by this method. Almost the same trends were observed for 1-aryl-1-alkylamines regarding the absolute configuration and chemical shift value in the ^{1}H NMR spectra. In the case of arylamines also, we found that the diastereomer showing the shielding effect was derived from the amine bearing the (*S*) configuration (Table 2, entry 1). Although the yields shown here are isolated yields after column chromatography, it is enough to determine the absolute configurations by use of crude products without purification, which are obtained in almost quantitative yields.

These shielding effects are not so effective from a viewpoint of the extent of high field shift in ^{1}H NMR spectra in contrast to the case of the existing CH/π interaction that we have already reported.[2] It can be assumed that the distances between the CH moiety and π plane are longer than those in the case of 2-aryl-1-cyclohexanols. In fact, the MM calculation[7] of **3a** suggested the absence of quite effective CH/π interaction due to the deviation between the π plane and CH moiety, as shown in Fig. 1.

On the other hand, (*R*)-isomer **4a** did not show the CH/π interaction completely in the MM calculation (Fig. 2).

We guess that this shielding effect was also responsible for the conformational restriction and the attraction of intramolecular van der Waals force between the CH and π moieties.

Needless to say that this methodology can be applied to the determination of the optical purity of various 1-aryl-1-alkylalcohol and amine analogues as a substitute for the chiral shift reagent strategy.[8]

Acknowledgements

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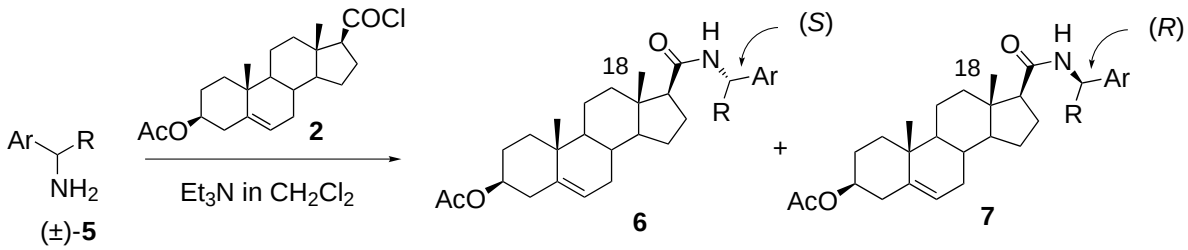
Table 2. ^{1}H NMR spectroscopic determination of the absolute configuration of 1-arylamines using CH/π shielding effect



Entry	Ar	R	Chemical shift of protons on C18–CH_3 in **3** or **4** [δ (ppm)][a]	Predicted configuration of resolved **5**	Yield (%)[b]
1	Ph	Me: **6a**	0.61	*S*[c]	71
	Ph	Me: **7a**	0.73	*R*	
2	*p*-Tolyl	Me: **6b**	0.62	*S**	69
	p-Tolyl	Me: **7b**	0.72	*R**	
3	4-Bromophenyl	Me: **6c**	0.58	*S**	78
	4-Bromophenyl	Me: **7c**	0.71	*R**	
4	2-Naphthyl	Me: **6d**	0.52	*S*[c]	68[d]
	2-Naphthyl	Me: **7d**	0.71	*R*[c]	71[d]
5	Ph	Et: **6e**	0.54	*S**	68
	Ph	Et: **7e**	0.73	*R**	

[a] 25°C in $CDCl_3$.
[b] Isolated yields of a mixture of diastereomers by column chromatography.
[c] The configuration was confirmed by use of an enantiomerically pure substrate with known absolute configuration.
[d] The enantiomerically pure (*S*)- and (*R*)-substrates were used because the racemic substrate is not commercially available.

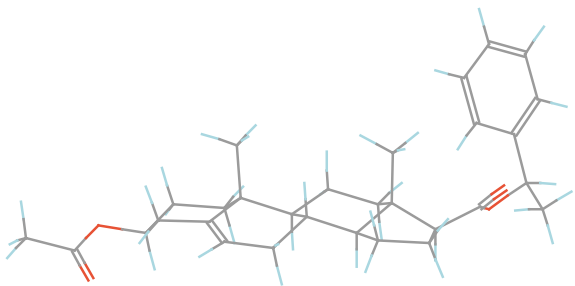


Figure 1. Calculated conformation of (*S*)-isomer **3a**.

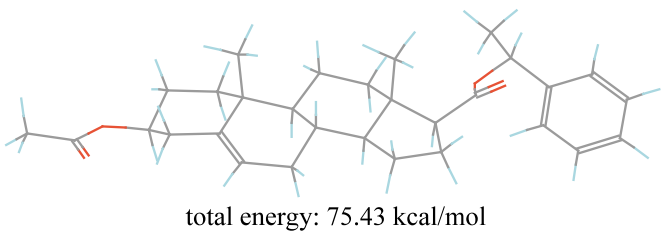


Figure 2. Calculated conformation of (*R*)-isomer **4a**.

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5. The numbering positions on the steroid ring and hexane ring are respectively depicted by the positions of 3β-acetoxy-Δ^5-etienic acid and 2-arylhexanols before esterification for the simple discussion.
6. Both (1*S*,2*R*) and (1*R*,2*S*) compounds are commercially available.
7. Two-dimensional structures of diastereomeric compounds **3a** and **4a** were converted to three-dimensional (3D) structures using Converter program in InsightII [(ver. 2000), Accelrys Inc., San Diego, CA.]. The obtained 3D structures were subjected to a systematic conformational search with an algorithm to eliminate the high energy conformations due to steric repulsion. In this study, the potential energy values of every accessible conformations (248,832 conformers) for each compound were calculated with a rotation increment of 30° for all the torsional angles of benzylester moiety by means of the molecular mechanics methods using Steepest Descent algorithm of Discover [(ver. 2.98, CVFF forcefield), Accelrys Inc., San Diego, CA.]. Then, 100 energy-lowest conformers for each compound having potential energies within 10 kcal/mol from the current global minimum were collected for the validation of conformational analysis. The obtained energy-low-

est conformer using Steepest Descent algorithm was optimized to evaluate the detailed conformational structure and total energy using Conjugate Gradient algorithm. The calculated structures and total energies were described in Fig. 1 and Fig. 2.

8. Recent examples: (a) Monchaud, D.; Lacour, J.; Coudret, C.; Fraysse, S. *J. Organomet. Chem.* **2001**, *624*, 388; (b) Watanabe, M.; Hasegawa, T.; Miyake, H.; Kojima, Y. *Chem. Lett.* **2001**, 4; (c) Ratni, H.; Jodry, J. J.; Lacour, J.; Kundig, E. P. *Organometallics* **2000**, *19*, 3997; (d) Inamoto, A.; Ogasawara, K.; Omata, K.; Kabuto, K.; Sasaki, Y. *Org. Lett.* **2000**, *2*, 3543.