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Magnetic shielding effect of amine and ammonium groups obtained from proton chemical shifts of androstane derivatives

Hajime Iwamoto, Yoshiaki Kondo, Takefumi Kawatani, Takeharu Haino and Yoshimasa Fukazawa*

Department of Chemistry, Graduate School of Science, Hiroshima University, Higashi-Hiroshima 739-8526, Japan

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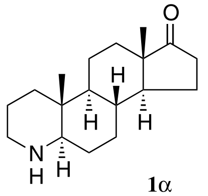
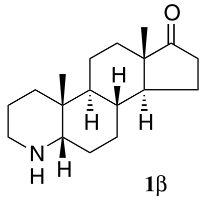
Abstract—4-Aza-5α-androstanone(**1α**) and 4-aza-5β-androstanone(**1β**) were synthesized in order to obtain the NMR shielding parameters for the secondary amine group. A combination of the electric field effect and the anisotropy of the magnetic susceptibility of the C–N bond can successfully reproduce the observed SIS values for these androstanes. Drastic chemical shift change of protons near-by nitrogen atom of ammonium salt was observed and shielding parameter for the secondary ammonium group was also obtained.

Conformational analysis in solution is very important for understanding physical and chemical properties of organic compound. While NMR techniques such as distance-dependent NOE[1] and torsion angle-dependent $^3J_{HH}$ coupling constants[2] were used extensively, it is not always satisfactory. Recently we have developed an efficient method,[3] which utilizes the substituent induced shifts (SIS) of polar functional groups. In the continuous effort to widen its applicability to a variety of organic compounds we have succeeded to develop the induced magnetic shielding parameters, for aromatic ring,[4] ether,[5] carbonyl,[6] lactone,[7] and by using them succeeded in conformational analysis of flexible molecules.[8] In this paper, we report the induced magnetic shielding parameters for the secondary amine group (C–NH–C) which is ubiquitous in organic compounds.

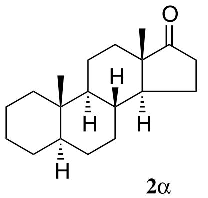
In order to obtain the reliable magnetic shielding parameters for this group, the steroid skeleton was chosen because of its rigidity and well defined geometry. Hence, we synthesized 4-aza-5α- (**1α**) and 4-aza-5β-androstanone (**1β**), and compared the chemical shifts of the associated protons with those of the corresponding reference compounds (**2α**, **2β**).



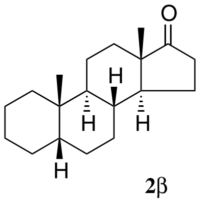
1α



1β



2α



2β

The synthesis of compound **1** is shown in Scheme 1. Protection of carbonyl groups of keto ester **3**,[9] which was obtained from 4-androstene-3,17-dion, followed by reduction of the ester group with $LiAlH_4$ in THF gave the corresponding primary alcohol. Tosylation of the primary alcohol, followed by the treatment of NaN_3 in DMF and 1 M HCl afforded primary azide **5**. Reduction of **5** using Pd/C in EtOH under hydrogen, followed by in situ cyclization gave imime **6**. Reduction of **6** with $LiAlH_4$ afforded the corresponding amine **7** as a mixture of diastereomer of C-5 position. Protection of secondary amino group of **7** with $(Boc)_2O$ in CH_2Cl_2, followed by tetrapropylammonium perruthenate (TPAP) oxidation[10] gave Boc protected amine **8**. HPLC separation of the mixture afforded **8α** and **8β** in a ratio of 5:2. The desired amine **1α** (4-aza-5α-androstan-17-one) and **1β** (4-aza-5β-androstan-17-one) was obtained from deprotection of Boc group, respectively. The structure of **1α** and **1β** was determined by X-ray crystallographic analysis (Fig. 1).[11]

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* Corresponding author. Tel.: +81-824-24-7427; fax: +81-824-24-0724; e-mail: fukazawa@sci.hiroshima-u.ac.jp

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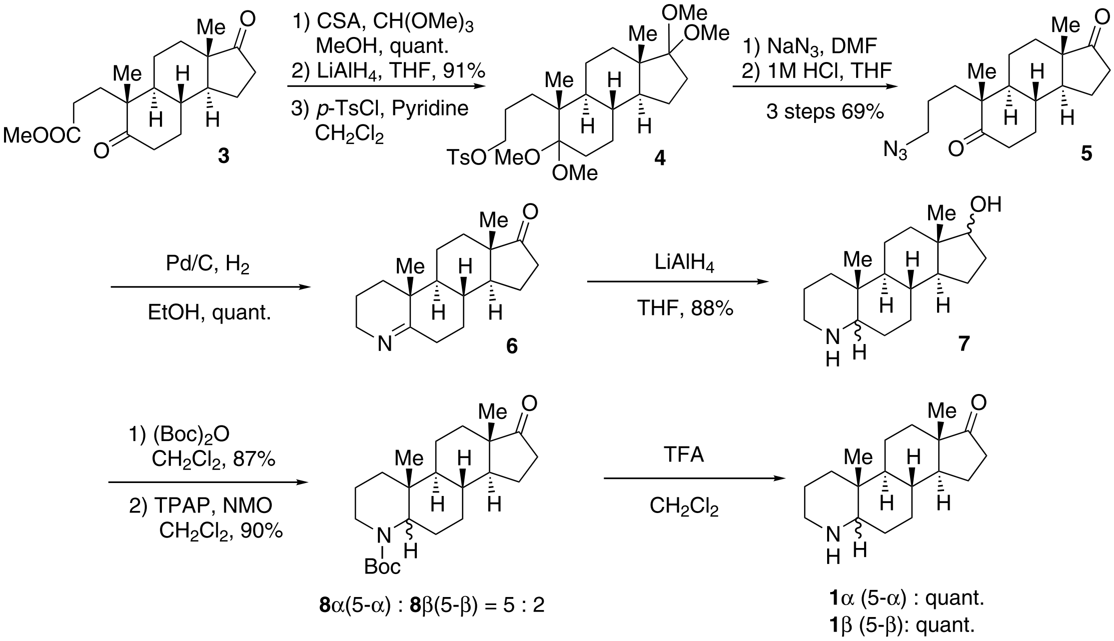

Scheme 1. Synthesis of 4-aza-5α-androstanone(**1α**) and 4-aza-5β-androstanone(**1β**).

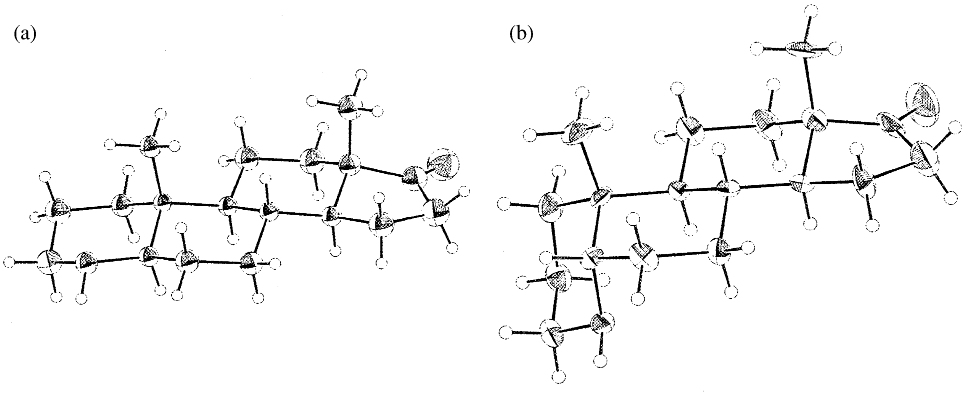

Figure 1. X-Ray crystal structure of (a) **1α** and (b) **1β**.

Assignments of the ^{1}H NMR signals for **1α** and **1β** in $CDCl_3$ solution were given using a combination of COSY, NOESY, HMBC and phase-sensitive DQF-COSY experiments. The observed SIS, which is defined as the change in chemical shift of a proton produced by the substituent, can be obtained by the chemical shift difference between **1** and **2**. The observed SIS values can be correctly reproduced by calculation if the set of correct shielding parameters and relative geometry of a proton with respect to the substituent are known. We utilized the X-ray structures to obtain such geometrical factor of the protons. As in the case of C–O–C group,[5] the substituent-induced chemical shift change of C–NH–C group can be described by the classical screening mechanisms,[12] with the sum of the electronic contribution parameters (κ_1 and κ_2), and those of the magnetic susceptibility ($\Delta\chi_1$ and $\Delta\chi_2$) of C–N bond. We used the axis system as shown in Figure 2. The origin of the three axes can be moved along the C–N bond to find the best-fit parameters. The reproduction of the observed SIS values was achieved by a multiple least-squares regression analysis. The correlation coefficient between the observed and calculated SIS values (R^2) is dependent on the distance (r) of the nitrogen atom from the origin (assumed center of the electric and induced magnetic dipole) along the C–N bond. The values of the shielding parameters and the correlation coefficient are also dependent on the structure.

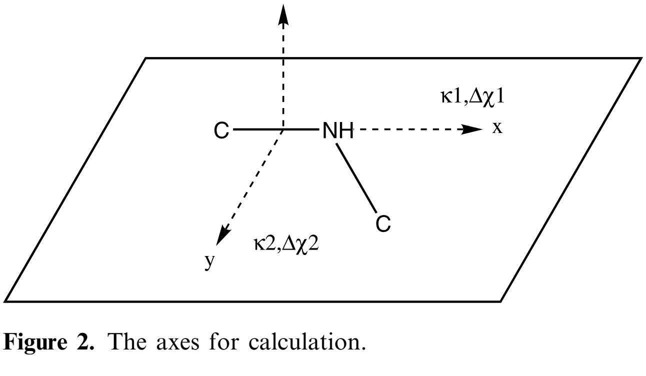

Figure 2. The axes for calculation.

Table 1. ^{1}H NMR chemical shifts[a] for compound **1α** and **1β** together with their observed and calculated SIS values

	Observed chemical shifts				Observed SIS			Calculated SIS		
Position	1α	1β	2α[b]	2β[b]	$\Delta\delta 1\alpha$	$\Delta\delta 1\beta$	$\Delta\delta 1\alpha$[c]	$\Delta\delta 1\beta$[d]	$\Delta\delta 1\alpha$[e]	$\Delta\delta 1\beta$[e]
1α	1.00	1.82	0.89	1.75	0.11	0.07	0.10	0.09	0.16	0.11
1β	1.73	0.99	1.67	0.91	0.06	0.08	0.05	0.16	0.10	0.18
2α	1.44	1.55	1.50	1.27	−0.06	0.28	0.02	0.20	0.02	0.22
2β	1.65	1.31	1.41	1.37	0.24	−0.06	0.15	0.02	0.20	0.04
3α	2.62	3.10	1.22	1.72	1.40	1.38	1.38	1.33	1.21	1.36
3β	3.05	2.63	1.65	1.21	1.40	1.42	1.38	1.39	1.75	1.41
5	2.22	2.45	1.07	1.31	1.15	1.14	1.19	1.22	1.25	1.25
6α	1.44	1.41	1.25	1.27	0.19	0	0.20	0.03	0.26	0.05
6β	1.38	1.90	1.25	1.90	0.13	0.14	0.21	0.25	0.26	0.27
7α	1.05	1.34	0.97	1.18	0.08	0.16	−0.02	0.11	0.01	0.13
7β	1.79	1.51	1.78	1.52	0.01	−0.01	0.03	0.03	0.07	0.05
8	1.55	1.61	1.55	1.58	0.00	0.03	0.02	0.00	0.06	0.02
9	0.73	1.80	0.72	1.47	0.01	0.33	−0.02	0.14	0.01	0.16
11α	1.65	1.56	1.67	1.55	−0.02	0.01	0.01	0.02	0.06	0.06
11β	1.30	1.27	1.27	1.26	0.03	0.01	0.01	0.04	0.06	0.04

[a] Measured in $CDCl_3$ at 25°C (500 MHz) and in ppm.
[b] Ref. 4.
[c] Calculated with parameters for **1α**.
[d] Calculated with parameters for **1β**.
[e] Calculated with parameters for both **1α** and **1β**.

While the best-fit values[13] for **1α** gave excellent correlation ($R^2=0.991$), those for **1β** value gave a lesser ($R^2=0.978$) value. The parameters for the two structures (**1α** and **1β**) gave a little bit smaller correlation coefficient [30 data set (range of the observed SIS values −0.06–1.42 ppm) $\Delta\delta_{obs}=a\cdot\Delta\delta_{calcd}+b$; $a=1.003$, $b=0.036$, $R^2=0.966$].[14] In Table 1, are listed the observed and calculated induced shift for the protons of the aza-steroids.

It is known that the induced magnetic shifts for an ammonium group are larger than those of the corresponding amine.[15] The values of the SIS of the secondary ammonium group can be obtained from the chemical shift differences of HCl salt of **1α** (**1α**·HCl) and **2α** (Table 2). They are very large when compared to those of the secondary amines. The values of the shielding parameters for the secondary ammonium group were also obtained from **1α**·HCl, the structure of which can be obtained from X-ray crystallographic analysis (Fig. 3).[16] In Table 2, the observed and calculated induced shift for the protons of **1α**·HCl are listed. Since the protons onto the carbon adjacent to the ammonium nitrogen suffer severe inductive influence from the positive charge of the adjacent ammonium group,[15] they are omitted from the shielding parameter calculation. A good correlation of these data is obtained in a linear regression analysis: [for 4-aza-5α-androstan-17-one hydrochloride, 14 data set (range of the observed SIS values 0–0.96 ppm) $\Delta\delta_{obs}=a\cdot\Delta\delta_{calcd}+b$; $a=0.967$, $b=0.015$, $R^2=0.943$].[17]

Table 2. ^{1}H NMR chemical shifts[a] for compound **1α** and **1α**·HCl together with their observed and calculated SIS values[b]

	Observed		Calculated SIS
Position	1α	$\Delta\delta 1\alpha$[b]	$\Delta\delta 1\alpha$
1α	1.12	0.23	0.21
1β	1.99	0.32	0.33
2α	1.73	0.23	0.18
2β	2.04	0.63	0.65
3α	3.46	2.24	[c]
3β	2.82	1.17	[c]
5	2.75	1.68	[c]
6α	2.21	0.96	0.86
6β	1.76	0.51	0.68
7α	1.09	0.12	0.08
7β	1.92	0.14	0.18
8	1.62	0.07	0.13
9	0.83	0.11	0.06
11α	1.67	0.00	0.06
11β	1.36	0.09	0.11
12α	1.26	0.03	0.01
12β	1.86	0.07	0.06

[a] Measured in $CDCl_3$ at 25°C (500 MHz) and in ppm.
[b] Ref. 4.
[c] These protons are omitted because of the close proximity to the substituents.

In conclusion, we have succeeded in obtaining new sets of parameters to estimate the induced magnetic shielding effect for both the secondary amine and ammonium groups, respectively. Furthermore, it is now clear that the contribution for the lone pair electrons of the nitrogen and N–H bond(s) is included in these shielding parameters and no need to add them explicitly.

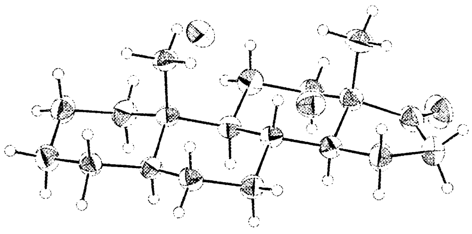

Figure 3. X-Ray crystal structure of **1α**·HCl·H_2O.

Acknowledgements

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11. The crystal data for **1α** and **1β** are as follows: **1α**: $C_{18}H_{29}NO$, FW = 275.43, orthorhombic, space group $P2_12_12_1$ a = 6.0500(1), b = 11.3920(3), c = 23.1830(8) Å, V = 1597.81(7) Å^3, and Z = 4; of 1818 total unique reflections, 1665 were considered observed at the level of $|F_o|>3.0\sigma|F_o|$. The structures were solved by the direct method (Sir 92). Full-matrix least squares refinements converged to a conventional R factor of 0.095, wR = 0.101. **1β**: $C_{18}H_{29}NO$, FW = 275.43, orthorhombic; space group $P2_12_12_1$ with a = 6.5340(2), b = 12.4320(1), c = 19.5590(7) Å, V = 1588.79(10) Å^3, and Z = 4; of 1895 total unique reflections, 1826 were considered observed at the level of $|F_o|>3.0\sigma|F_o|$. R = 0.1235, wR^2 = 0.1176. Supplementary crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 210952 for **1α** and No. CCDC 210971 for **1β**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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13. The values for **1α** are: r = 1.35 Å, $\kappa_1 = -1.80\times10^{-12}$ esu, $\kappa_2 = -0.19\times10^{-12}$ esu, $\Delta\chi_1 = -3.07\times10^{-30}$ cm^3/molecule, $\Delta\chi_2 = 0.82\times10^{-30}$ cm^3/molecule, $\Delta\delta_{\text{othes}} = 2.01\times10^{-8}$. Those for **1β** are: r = 1.30 Å, $\kappa_1 = -1.73\times10^{-12}$ esu, $\kappa_2 = 0.18\times10^{-12}$ esu, $\Delta\chi_1 = -3.92\times10^{-30}$ cm^3/molecule, $\Delta\chi_2 = 0.70\times10^{-30}$ cm^3/molecule, $\Delta\delta_{\text{othes}} = -0.70\times10^{-8}$.
14. The values of amine group for the best fit set are: r = 1.30 Å, $\kappa_1 = -1.77\times10^{-12}$ esu, $\kappa_2 = -0.20\times10^{-14}$ esu, $\Delta\chi_1 = -3.49\times10^{-30}$ cm^3/molecule, $\Delta\chi_2 = -0.76\times10^{-30}$ cm^3/molecule, $\Delta\delta_{\text{othes}} = 0.66\times10^{-8}$.
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16. The crystal data for **1α**·HCl·H_2O are as follows; **1α**·HCl·H_2O; $C_{18}H_{32}ClNO_2$, FW = 329.91, orthorhombic, space group $P2_12_12_1$ with a = 6.7460(2), b = 8.7340(2), c = 30.376(1) Å, V = 1789.74(9) Å^3, and Z = 4; of 1953 total unique reflections, 1894 were considered observed at the level of $|F_o|>3.0\sigma|F_o|$. The structures were solved by the direct method (Sir 92). Full-matrix least squares refinements converged to a conventional R factor of 0.047, wR = 0.058. Crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 210972.
17. The values of ammonium group for the best fit set are: r = 0.40 Å, $\kappa_1 = -8.94\times10^{-12}$ esu, $\kappa_2 = -6.25\times10^{-12}$ esu, $\Delta\chi_1 = -8.47\times10^{-30}$ cm^3/molecule, $\Delta\chi_2 = -2.78\times10^{-30}$ cm^3/molecule, $\Delta\delta_{\text{othes}} = 0.92\times10^{-8}$.