Pergamon

Tetrahedron, Vol. 52, No. 7, pp. 2325-2336, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01059-9

Shielding Effect of Ether C-O Bond Obtained from Proton Chemical Shifts of 4-Oxa-5α- and 4-oxa-5β-androstan-17-ones

Yanyan Yang, Takeharu Haino, Shuji Usui, and Yoshimasa Fukazawa*
Department of Chemistry, Faculty of Science, Hiroshima University, Higashi-Hiroshima 739, Japan

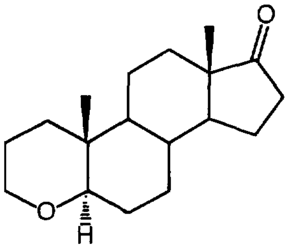
Abstract: 4-Oxa-5α- and 4-oxa-5β-androstanones (**1** and **2**) were synthesized in order to obtain the NMR shielding parameters for the ether C-O bond. The complete NMR assignment of both the proton and carbon atoms for these compounds and substituent-induced shifts (SIS) from the corresponding androstanones (**3** and **4**) are presented. The comparison of the molecular structure obtained by MM3 calculation with that of X-ray crystallographic analysis disclosed that the former structure is completely superimposable to the latter in both of the compounds **1** and **2**. A combination of the electric field effect and the anisotropy of the magnetic susceptibility of the C-O bond can successfully reproduced the observed SIS values for these androstanones.

INTRODUCTION

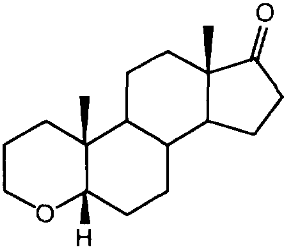
Conformational analysis of a macrocyclic compound is not straightforward because it is extremely flexible with many conformational options. Although the X-ray analysis is the most promising method to know the precise structure, it provides only limited number of geometries in the solid state. On the other hand, NMR spectroscopy affords much useful information for not only the structures of conformers in solution but also the dynamic equilibrium between them. Freezing the conformational equilibrium, which is the common method for analysis, is often not effective in highly flexible molecules. We have developed a useful and very reliable method for the conformational analysis of such a flexible molecule without using the freezing technique.[1] The method utilizes a chemical shift simulation for all the plausible conformers obtained by molecular mechanics calculations. For this method, information is necessary not only on the structures of dynamically equilibrating conformers but also on the calculated chemical shifts of the protons of these conformers. Hence, our method deeply depends on the accuracy of the calculated chemical shifts. The calculation of the chemical shift can be achieved by the estimation of the change in chemical shift of proton produced by nearby substituents.[2-4] However, the parameters of shielding effect for substituents are rather limited, and hence, it restricts the application of this conformational analysis method to a wide variety of compounds. In our previous paper we have reported new parameters of shielding effect of carbonyl group,[5] and by using them we have succeeded in determining the preferred conformers of [3.3]metacyclophanedione,[6] which is a twelve membered ring compound having two benzenes and two carbonyl groups. To widen the applicability of the method of chemical shift simulation to heteroatom-containing compounds, it is necessary to obtain the shielding parameters for other substituents such as an ether C-O bond which is frequently found in many organic compounds.

Several parameters for the shielding effect of the ether C-O bond have been reported so far.[3,7-10] Pople's parameters were derived from the calculation based on molecular orbital theory using both diamagnetic and paramagnetic contribution for atoms.[7] Zürcher proposed the parameters of shielding effect of C-O bond using several hydroxy androstanes. In his calculation, the effect of C-OH group instead of C-O bond was estimated and the electric field effect of the dipolar O-H group was neglected.[3] The other reported parameters[8-10] were derived from the chemical shift differences of only limited number of protons with ignorance of the electric field effect of dipole of C-O bond.

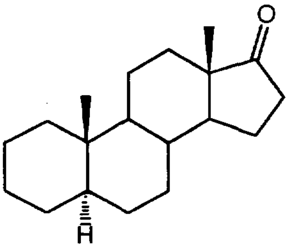
To obtain the reliable shielding parameters of ether C-O bond, steroid skeleton was chosen because of its rigidity and well known geometry. Hence, we synthesized 4-oxa-5α- and 4-oxa-5β-androstanones (**1** and **2**) and compared their chemical shifts with those of the corresponding reference compounds (**3** and **4**). Now we report our new NMR shielding parameters of ether C-O bond.



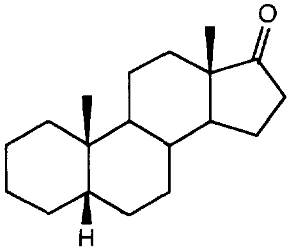
1



2



3



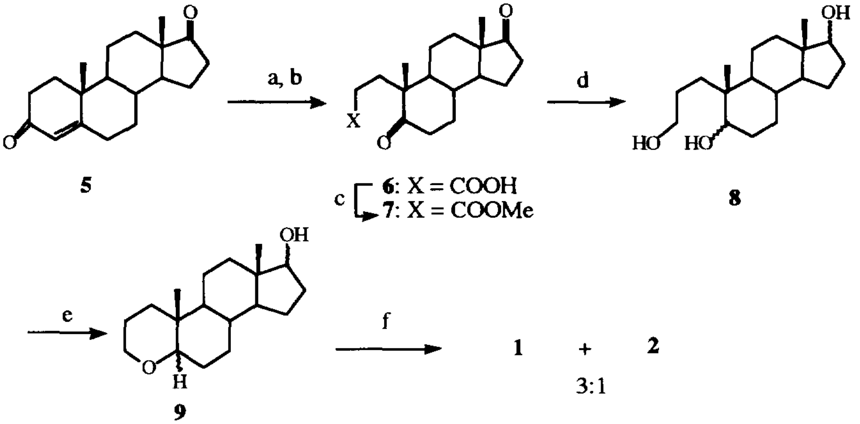
4

RESULTS AND DISCUSSIONS

Synthesis

The synthesis of 4-oxa-5α- and 4-oxa-5β-androstan-17-ones (**1** and **2**) is shown in Scheme 1. Ozonolysis[11] of 4-androstene-3,17-dione (**5**) and subsequent *in situ* treatment of the resulting ozonide with H_2O_2 yielded keto-acid (**6**). Treatment of the acid **6** with diazomethane gave methyl ester (**7**). Reduction of **7** with $LiAlH_4$ in THF gave a mixture of four diastereomers of alcohol (**8**). Selective tosylation of primary alcohol of the mixture and subsequent intramolecular ether formation furnished a mixture of 4-oxandrostan-17-ols (**9**). The mixture **9** was oxidized using PCC to give a diastereomeric mixture of desired ketones (**1** and **2**). HPLC separation of the mixture afforded 4-oxa-5α-androstan-17-one (**1**) and 4-oxa-5β-androstan-17-one (**2**) in a ratio of 3:1. The preparation of the reference compounds (**3** and **4**) was carried out by a reported procedure.[12, 13] The structures and the stereochemistry of **1** and **2** were confirmed by X-ray crystallographic analysis (Figure 1).

Scheme 1.



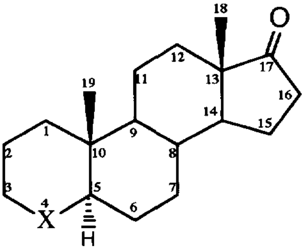
a) O_3, AcOH-AcOEt. b) 30% H_2O_2. c) CH_2N_2 ether, 93% from **5**. d) $LiAlH_4$, THF, 97%. e) *p*-TsCl, pyridine, CH_2Cl_2, 31%. f) PCC, CH_2Cl_2, >99%.

Assignments of NMR Spectroscopy

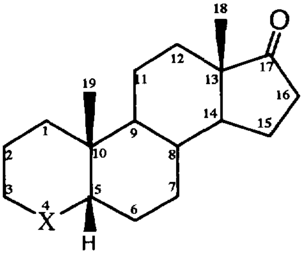
Assignment of ^1H- and ^{13}C-NMR signals was mainly based on connectivity information from homo- and heteronuclear scalar couplings. Assignment of ^1H signals for 4-oxa-5α- and 4-oxa-5β-androstanones in $CDCl_3$ solution was made using a combination of COSY (correlated spectroscopy), NOESY (nuclear Overhouser enhancement spectroscopy), HMBC (heteronuclear multiple bond corrlation), and phase sensitive DQF-COSY (double quantum filtered COSY) experiments. Assignment of ^{13}C signals was carried out using a combination of DEPT (distortionless enhancement by polarization transfer), ^{13}C-^1H shift correlation, and HMBC. These measurements gave additional support for the ^1H assignment. The 500 MHz ^1H-NMR spectra for **1** and **2** exhibited some readily assignable signals such as two angular methyls, the methine carrying oxygen (C5), the oxymethylene (C3), and the methylene (C16) vicinal to the carbonyl group. The chemical shift of 18-methyl was unambiguously assigned from the ^1H-^{13}C long-range correlation with ^{13}C of the carbonyl (C17) obtained from a HMBC experiment. Starting from the 16βH signal, which was confirmed by a strong NOE with 18-Me, all the ^1H-^1H connectivities were unambiguously assigned using the above mentioned techniques. The signals of C1-C3 protons were similarly assigned.

Although the procedure of NMR analysis of all the compounds was almost the same, the assignment of 5β-androstan-17-one (**4**) was not straightforward as those of the compound **1** and **2**. The ^{13}C chemical shifts of C4, C6 and C7 are not so different with each other and they are within 0.2 ppm. The proton signals of 2α, 6β, 11β and 12α are heavily overlapped at around δ 1.27 and also those of 3β and 4β were superimposed at δ 1.72. Phase sensitive DQF-COSY spectrum gave an effective connectivity information of the overlapped protons. The complete assignment of the sequence was confirmed by the analysis of the DQF spectrum. All assignments of ^1H NMR are shown in Table 1 and those of ^{13}C-NMR in the experimental section (Table 3).

The observed substituent-induced shifts (SIS), which is defined as the change in chemical shift of a proton in a C-H bond produced by the substituent, can be obtained by the chemical shift difference of these compounds.



1. X = O
3. X = CH_2



2. X = O
4. X = CH_2

Table 1. ^{1}H NMR Shifts in 5α– and 5β-Androstanones. [a]

position	**3**[b]	**1**	$\Delta\delta_{5\alpha}$[c]	**4**	**2**	$\Delta\delta_{5\beta}$[d]
1α	0.89	1.12	0.23	1.75	1.88	0.13
1β	1.67	1.76	0.08	0.91	1.11	0.20
2α	1.50	1.40	-0.10	1.27	1.77	0.50
2β	1.41	1.85	0.44	1.37	1.28	-0.09
3α	1.22	3.43	2.21	1.72	4.01	2.29
3β	1.65	3.98	2.32	1.21	3.41	2.20
4α	1.29			1.72		
4β	1.29			1.22		
5	1.07	2.94	1.88	1.31	3.14	1.83
6α	1.25	1.63	0.37	1.27	1.76	0.49
6β	1.25	1.47	0.21	1.90	1.66	-0.24
7α	0.97	1.03	0.06	1.18	1.31	0.13
7β	1.78	1.82	0.05	1.52	1.52	0.00
8	1.55	1.54	-0.01	1.58	1.58	0.00
9	0.72	0.72	0.00	1.47	1.71	0.24
11α	1.67	1.63	-0.03	1.55	1.58	0.03
11β	1.27	1.31	0.05	1.26	1.29	0.03
12α	1.23	1.21	-0.01	1.27	1.34	0.07
12β	1.79	1.80	0.00	1.80	1.82	0.02
14	1.27	1.24	-0.03	1.36	1.39	0.03
15α	1.91	1.92	-0.01	1.93	1.95	0.02
15β	1.60	1.50	0.00	1.49	1.52	0.03
16α	2.03	2.07	0.01	2.06	2.08	0.02
16β	2.45	2.44	0.01	2.43	2.44	0.01
18	0.86	0.87	0.01	0.85	0.86	0.01
19	0.81	0.96	0.15	0.95	0.85	-0.10

[a] Measured in $CDCl_3$ at 25 ℃ (500 MHz) and in ppm. [b] Reference 4. [c] $\Delta\delta_{5\alpha} = \delta_1 - \delta_3$. [d] $\Delta\delta_{5\beta} = \delta_2 - \delta_4$.

Molecular Structures of Androstan-17-ones

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. In order to obtain such

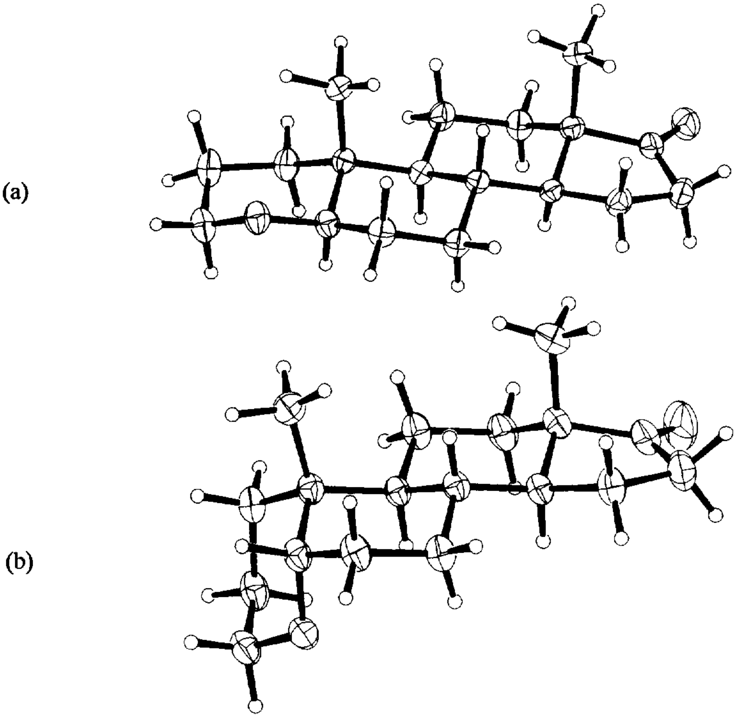


Figure 1. ORTEP drawing of **1** (a) and **2** (b).

geometrical factor of the proton we have to get precise molecular structures. It is known that the structure obtained by an X-ray crystallographic analysis has lesser positional accuracy of protons than that of heavier elements. On the other hand, there is no such shortcoming in molecular mechanics calculation. We therefore applied MM3 calculation[14] to obtain geometrical factors of protons for these compounds. The reliability of the calculated structures can be estimated by comparison of the coordinates of the heavier atoms with those of the observed. A superimposed analysis of the two structures for respective compounds was carried out, in which the root mean square deviations of the 20 non-hydrogen atoms between the calculated and observed structures are 0.045 Å for **1** and 0.024 Å for **2**, respectively. The result suggested that the structures obtained by MM3 calculation are nearly completely identical with those of the observed and can be used to calculate the shielding effect of the ether C-O bond. Next, we estimated geometrical change due to the replacement of $-CH_2-$ by -O- group. The calculated geometries of **1** and **2** were then compared with those of **3** and **4**. The similar superimposed analyses gave the rmsd of 0.003 Å and 0.004 Å, respectively, showing few geometrical changes caused by the replacement of CH_2 by oxygen atom.

Calculation of the Substituent-Induced Chemical Shift for Ether C-O Bond

The replacement of a CH_2 group by other fuctionalities may cause appreciable chemical shift changes of nearby protons. The substituent-induced chemical shift change can be described by classical screening mechanisms as

$$\Delta\delta = \Delta\delta_{el} + \Delta\delta_{magn} + \Delta\delta_{others} \qquad (1)$$

where $\Delta\delta_{el}$ and $\Delta\delta_{magn}$ are the chemical shifts difference from electric field effect due to the dipole moment of the substituent, and the contribution of the anisotropy of the magnetic susceptibility. $\Delta\delta_{others}$ is the contribution of other factors mainly derived from van der Waals interaction between the substituent and the proton and solvent effect. The electric contribution for SIS value, $\Delta\delta_{el}$, can be estimated by using the Buckingham equation (2),[15]

$$\Delta\delta_{el} = \kappa e_{CH} \qquad (2)$$

where κ is a constant to be determined by experiment and e_{CH} is the geometrical factor for the proton. The geometrical factor can be estimated by relative arrangement of the C-H bond with respect to the substituent. The contribution of the anisotropy of the magnetic susceptibility, $\Delta\delta_{magn}$ can be represented by using McConnell equation (3),[16]

$$\Delta\delta_{magn} = \Delta\chi(1 - 3\cos^2\theta)/3r^3 \qquad (3)$$

where $\Delta\chi$ is a difference between the magnetic susceptibilities of bonds in different directions, r is the distance between the proton and the dipole of the substituent and θ is the angle between the axis of the dipole and the distance vector of the proton. For a nonaxial symmetric dipole, such as C-O-C, it is necessary to take $\Delta\chi_1$ and $\Delta\chi_2$ for susceptibility difference:

$$\Delta\delta_{magn} = \{(\Delta\chi_1^{C-O-C}(1 - 3\cos^2\theta) + \Delta\chi_2^{C-O-C}(1 - 3\cos^2\theta)\}/3r^3 \qquad (4)$$

We set three axes as shown in Figure 2: X axis is on the C-O bond, Y axis is vertical to the C-O bond and in the C-O-C plane, and Z axis is vertical to the C-O-C plane. The origin of the three axes can be moved along the C-O bond to find best fit parameters.

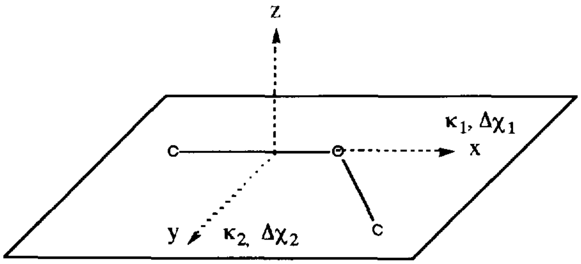
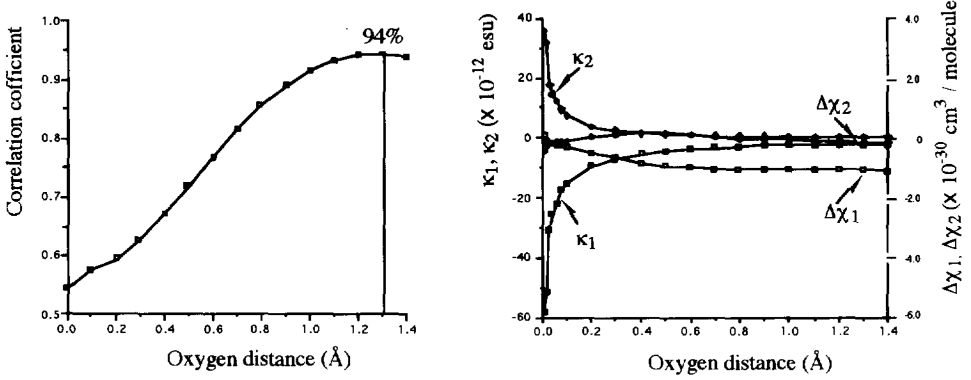


Figure 2. The axes for calculation.

The reproduction of the observed SIS values was carried out by a multiple least-squares regression analysis using the above mentioned equations and the geometrical factors obtained by the MM3 calculations. Initially, an attempt was tried with a reduced model assuming that only one of the two major contributors ($\Delta\delta_{el}$ and $\Delta\delta_{magn}$) is operative. However, it was impossible to obtain a good fit with the experimental values if only one factor is assumed to be responsible for the SIS values: the correlation coefficients of linear regression analyses between the observed and calculated SIS values are 0.54 for the electric field effect alone and 0.84 for only the anisotropy of the magnetic susceptibility, respectively. Better fits were obtained with a model in which both mechanisms are simultaneously operative.

The correlation coefficients between the observed and calculated SIS values within the multiple regression analyses are dependent on the distance of the oxygen atom from the origin (assumed center of the electric and



(a) (b)

Figure 3. Correlation coefficients (a) and $\kappa_{c\text{-}o}$ and $\Delta\chi_{c\text{-}o}$ (b) as a function of the distance of the oxygen atom from the origin along the C-O axis.

induced magnetic dipole) along one of the C-O bonds (Figure 3a). As is clearly seen a maximum is obtained at the distance of 1.3 Å from the oxygen atom. The values of the shielding parameters are also dependent on the distance (Figure 3b). The values for the best fit set are:

κ_1 = -2.39×10^{-12} esu

κ_2 = 0.19×10^{-12} esu

$\Delta\chi_1$ = -10.85×10^{-30} cm^3/molecule

$\Delta\chi_2$ = -1.39×10^{-30} cm^3/molecule

$\Delta\delta_{others}$ = 1.0×10^{-8}

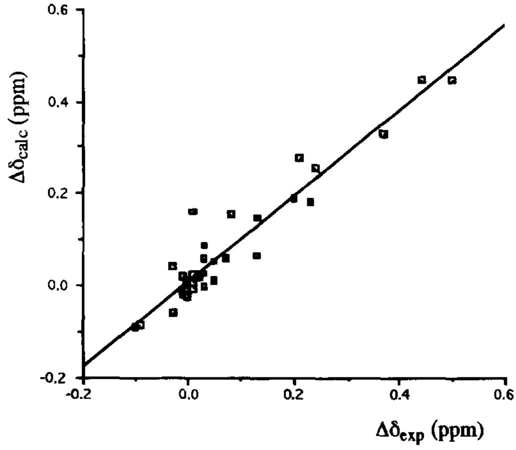


Figure 4. Experimental vs. calculated SIS values.

With the best fit NMR shielding parameters, we calculated the SIS values for all the protons of 4-oxa-5α- and 4-oxa-5β-androstan-17-ones and compared with those of observed. In Table 2, the observed and calculated induced shift for all the protons of the oxasteroids are listed. Excellent correlation of these data is obtained in a linear regression analysis, where some of the protons are omitted because of the close proximity to the substituents: [for 4-oxa-5α- and 4-oxa-5β-androstan-17-ones, 36 data set (range of the observed SIS values -0.10 ~ 0.50 ppm) $\Delta\delta_{calc} = a\bullet\Delta\delta_{obs} + b$; $a = 0.943$, $b = 0.010$, $R^2 = 0.943$].

Table 2. The Observed and Calculated Induced Shifts of 4-Oxa-5α- and 4-oxa-5β-androstan-17-ones (**1** and **2**).

position	**1**		**2**	
	obsd.	calcd.	obsd.	calcd.
1α	0.23	0.19	0.13	0.14
1β	0.08	0.15	0.20	0.20
2α	-0.10	-0.07	0.50	0.41
2β	0.44	0.41	-0.09	-0.07
6α	0.37	0.35	0.49	0.33
6β	0.21	0.31	-0.24	-0.08
7α	0.06	-0.09	0.13	0.08
7β	0.05	0.03	0.00	0.01
8	-0.01	0.03	0.00	-0.03
9	0.00	-0.11	0.24	0.24
11α	-0.03	0.04	0.03	0.08
11β	0.05	0.05	0.03	0.02
12α	-0.01	-0.01	0.07	0.05
12β	0.00	0.02	0.02	0.02
14	-0.03	-0.05	0.03	0.06
15α	-0.01	-0.02	0.02	0.02
15β	0.00	-0.00	0.03	-0.00
16α	0.01	-0.00	0.02	0.02
16β	0.01	0.00	0.01	0.01
18	0.01	0.02	0.01	0.02
19	0.15	0.35	-0.10	-0.14

As is clarified by this analysis, a quantitative prediction of SIS value for a certain proton can be done only if the geometrical factor of the proton is provided. To calculate the geometrical factor of the proton, relative dispositions for not only the proton but also the carbon atom on which the proton is attached should be known. This is because of the electric contribution term for the SIS calculation. On the other hand, the contribution of the anisotropy of the magnetic susceptibility is dependent only the relative position for the proton with respect to the substituent. As the result of this analysis, it is shown that the magnetic anisotropy of the substituent is the major contributor since it gave the high correlation coefficient (0.84) of the regression analysis compared to the maximum (0.94). The qualitative shielding region for the C-O-C group can then be expressed by the diamagnetic anisotropy as shown in Figure 5. These maps should be useful for judging the sign and magnitude of the SIS value for a certain nearby proton of any C-O-C group.

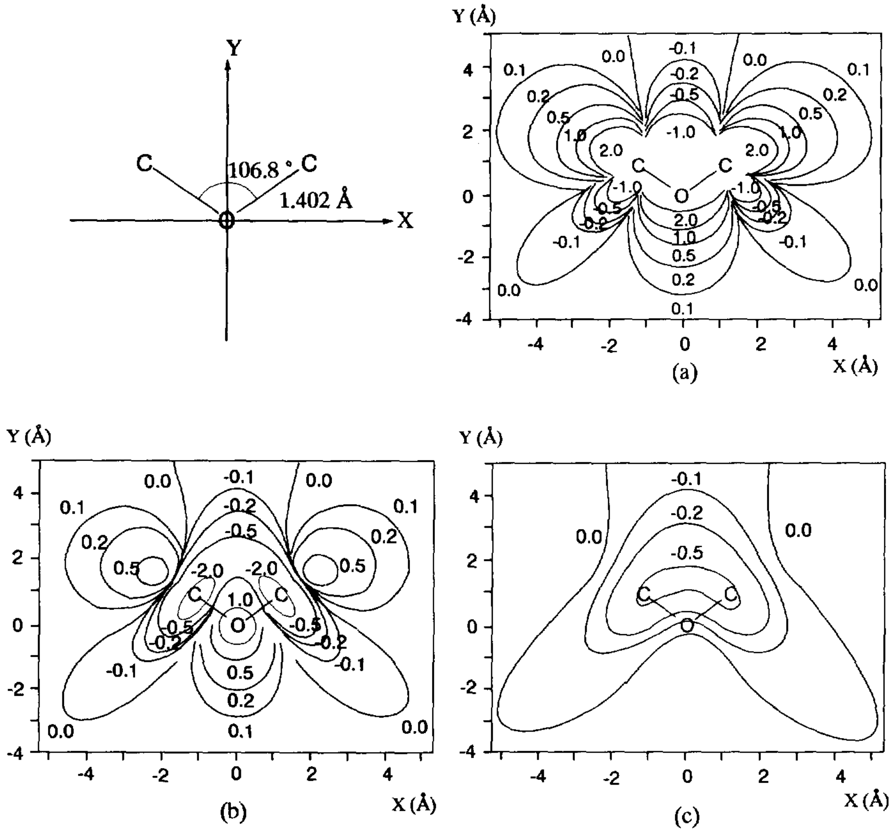


Figure 5. Vertical sections of the shielding zone for ether C-O-C group (ppm; a minus sign denotes down field shift). (a) Z = 0.0 Å. (b) Z = 1.0 Å. (c) Z = 2.0 Å.

CONCLUSION

By use of 2D NMR techniques such as ^{13}C-^{1}H COSY, ^{1}H-^{1}H COSY, DQF-COSY, HMBC, the complete assignments of ^{1}H and ^{13}C for the compounds **1**, **2**, and **4**, were successfully carried out. A new set of shielding parameters for ether C-O bond was obtained, with which a high correlation coefficient (0.943) between the observed and calculated SIS values for these androstanones was given. It is found that both the magnetic anisotropy and the electric dipole of the substituent are operative however, the former is the major factor. A qualitative magnetic shielding zone of the C-O-C group is given by use of the contribution of the magnetic anisotropy of the substituent.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra at high field were recorded with a JEOL-GSX500 and JEOL-GSX270 NMR spectrometer at 500 and 270 MHz (^{1}H NMR) and 125.65 MHz and 67.8 MHz (^{13}C NMR). Sample concentrations in $CDCl_3$ were 0.05 ~ 0.1 M for most 1D experiments for NOE and 2D measurements. All melting points were determined with a micro melting apparatus (Yanagimoto) and are uncorrected. HPLC were operated with a CCPS (TOSOH). Recycling preparative GPLC were performed with a LC-908s (JAI). IR spectra were measured using a Hitachi 260-10s infrared spectrophotometer. The mass spectra were taken with a JEOL JMS-SX 102A high-resolution double-focusing mass spectrometer at the Instrument Center for Chemical Analysis, Hiroshima University.

One-dimensional NOE difference experiments were run automatically by using a microprogram based on the method of Hall and Sanders[17] (PD = 5s). Two-dimensional NOESY and COSY experiments were performed in absolute mode, and DQF-COSY experiment was carried out in phase sensitive mode. All 2D NMR experiments were obtained using the standard pulse programs and sequences.

Synthetic Procedure

Methyl 5,17-dioxo-A-nor-3,4-seco-androstan-3-oate (7). Ozonolysis of 4-androstene-3,17-dione (2.0 g, 6.98 mmol) on Turner's method[11] and subsequent *in situ* treatment of the resulting ozonide with 30% H_2O_2 gave 5,17-dioxo-*A*-nor-3,4-seco-androstan-3-oic acid (**6**, 1.99 g, 93%) as a colorless oil; IR ($CDCl_3$) 2940, 1730, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.94 (s), 1.56 (s), 1.20~1.41 (m), 1.47~1.76 (m), 1.78~2.72 (m), 5.72 (s); ^{13}C NMR ($CDCl_3$) δ=13.70, 20.34, 20.68, 21.75, 29.02, 29.17, 29.88, 30.90, 34.38, 35.64, 37.64, 47.60, 47.94, 50.43, 50.66, 178.83, 214.21, 220.30. MS *m/z* 306 (M^+).

An ether solution (10 cm^3) of diazomethane from nitrosomethylurea (1.0 g) was added slowly to **6** (152 mg, 0.496 mmol) at 0 °C, then stirred for over night at room temperature, and the solution was evaporate to afford **7** (159 mg, >99%) as a colorless oil; IR ($CDCl_3$) 2940, 1724, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.94 (s), 1.15 (s), 1.15~1.41 (m), 1.47~1.72 (m), 1.82~2.40 (m), 2.42~2.67 (m), 3.66 (s); ^{13}C NMR ($CDCl_3$) δ=13.70, 20.42, 20.66, 21.75, 20.07, 29.43, 29.86, 30.96, 34.38, 35.61, 37.64, 47.54, 47.83, 50.40, 50.70, 51.54, 174.15, 213.76, 219.90. HRMS calcd for $C_{19}H_{28}O_4$: 320.1976, found: 320.1988.

A mixture of diastereomers for A-Nor-3,4-seco-androstane-3,5,17-triol (8). To a suspension of $LiAlH_4$ (600 mg, 15.8 mmol) in THF (40 cm^3) was added dropwise to a solution of ester **7** (1.51 g, 4.71 mmol) in THF (40 cm^3). The mixture was stirred at room temperature for 24 h and then was quenched with saturated Na_2SO_4 aq. After filtration, the filtrate was drived over $MgSO_4$ and concentrated to give a mixture of diastereomers as colorless powder (1.34 g, 97%); mp 287-288 °C; IR (KBr) 3350, 2930, 2860 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.73 (s), 0.75(s), 0.84 (s), 0.86 (m), 0.73~1.88 (m), 1.98~2.12 (m), 3.43~3.79 (m); ^{13}C NMR ($CDCl_3$) δ=11.04, 15.09, 20.66, 23.40, 24.97, 29.40, 29.82, 30.03, 30.50, 31.22, 34.77, 36.59, 40.56, 42.91, 46.01, 47.51, 50.89, 62.82, 63.62, 72.89, 81.86. HRMS calcd for $C_{18}H_{32}O_3$: 296.2365, found: 296.2351.

A mixture of diastereomers for 4-Oxandrostan-17-ol (9). To a solution of **8** (1.39 g, 4.68 mmol) in CH_2Cl_2 (300 cm^3) was added pyridine (30 cm^3) and *p*-toluenesulfonyl chloride (0.984 g, 5.16 mmol) at 0 °C. After refluxing for 1.5 h, the reaction mixture was stirred at room temperature for overnight. The mixture was extracted with ether, washed by 5% $CuSO_4$ aq and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel and then by recycling preparative GPLC ($CHCl_3$) to give a mixture of diastereomers **9** as colorless powder (404 mg, 31%); mp 182-183.5 °C; IR (KBr) 3350, 2930, 2850 cm^{-1}; ^1H NMR (270 MHz) δ=0.60~0.73 (m), 0.73 (s), 0.83 (s), 0.83~1.01 (m), 0.94 (s), 1.01~1.98 (m), 1.98~2.14 (m), 2.92 (dd, J= 4.5 Hz and 12 Hz), 3.12 (t, J= 3 Hz), 3.37~3.47 (m), 3.62 (t, J= 8.5 Hz), 3.97 (dd, J =5.4 Hz and 11 Hz); ^{13}C NMR ($CDCl_3$) δ=11.1, 12.6, 20.0, 21.4, 22.1, 22.8, 23.3, 23.4, 25.5, 27.2, 27.4, 29.4, 30.5, 30.6, 34.5, 34.9, 35.2, 36.4, 36.5, 36.9, 40.6, 43.1, 50.7, 52.0, 68.9, 69.0, 81.8, 81.9, 82.6, 84.9. HRMS calcd for $C_{18}H_{30}O_2$: 278.2233, found: 278.2246.

4-Oxa-5α- and 4-Oxa-5β-androstan-17-one (1 and 2). A solution of **9** (100 mg, 0.359 mmol) in CH_2Cl_2 (10 cm^3) was added to a mixture of PCC (pyridium chlorochromate, 116 mg, 0.538 mmol) and Celite 545 (80 mg) in CH_2Cl_2 (10 cm^3). The mixture was stirred at room temperature for 3 h and then Florisil (100~200 mesh) was added. After filtration, the filtrate was concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give colorless powder (101 mg, >99%) in a mixture of **1** and **2** (3:1). Further purification by HPLC (Wakosil 5Sil, 10.0X150 mm, 4% *i*-propanol-hexane) afforded pure sample of **1** and **2**, respectively. **1**: Colorless prisms from isopropanol-cyclohexane; mp 110-112 °C; IR (KBr) 2930, 2840, 1722 cm^{-1}. Anal. Found: C, 78.05; H, 10.12 %. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21%. **2**: Colorless prisms from *i*-propanol-cyclohexane; mp 101-103 °C; IR (KBr) 2930, 2840, 1722 cm^{-1}. Anal. Found: C, 78.26; H, 10.22 %. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21%.

Table 3. ^{13}C NMR Shifts in 5α- and 5β-Androstanones. [a]

position	1	2	3[b]	4
1	36.2	34.5	38.7	37.6
2	22.6	22.0	22.1	21.3
3	68.9	68.8	26.7	27.0
4			28.7	27.1
5	84.5	82.3	47.1	43.7
6	27.0	27.0	29.0	27.2
7	28.5	24.7	31.0	25.5
8	34.3	34.7	35.1	35.5
9	51.8	40.6	54.9	40.9
10	36.3	35.3	36.4	35.6
11	19.6	20.0	20.1	20.1
12	31.2	31.7	31.6	31.8
13	47.7	47.8	47.8	47.9
14	50.9	51.1	51.6	51.6
15	21.6	21.8	21.8	21.8
16	35.6	35.9	35.9	36.0
17	220.7	221.3	221.5	221.6
18	13.7	13.7	13.8	13.8
19	12.4	21.3	12.2	24.2

[a] Measured in $CDCl_3$ at 25 ℃ (500 MHz) and in ppm. [b] Reference 18.

X-ray Diffraction Analysis of 1 and 2.

The crystal data for **1** and **2** are as follows; **1**: Monoclinic; space group $P2_1$ with a = 13.566 (2), b = 6.436 (1), c = 9.334 (2) Å, β = 105.54 (1)°, V = 785.2 (3) Å^3, and Z = 2; **2**: Orthorhombic; space group $P2_12_12_1$ with a = 12.526 (2), b = 19.199 (3), c = 6.510 (1) Å, V = 1565.6 (4) Å^3, and Z = 4. The empirical formula is $C_{18}H_{28}O_2$, molecular weight is 276.40, and calculated density is 1.17 g/cm^3. The three-dimensional X-ray data were collected by the use of graphite-monochromated Cu Kα radiation (λ=1.54178 Å) on a Mac Science MXC3 automatic four-circle diffractometer up to a maximum 2θ of 130.0°. Of 1437 (for **1**) and 1538 (for **2**) total unique reflections, 1430 (for **1**) and 1490 (for **2**) were considered observed at the level of $|F_o|>3.0\sigma|F_o|$ (for **1**) and $|F_o|>4.0\sigma|F_o|$ (for **2**), respectively. The structures were solved by the direct method (SHELXS78). All non-hydrogen atoms were located on the initial E synthesis. Hydrogen atoms were found from the difference fourier map and included in the further calculations. Full-matrix least squares refinements with anisotropic 20 non-hydrogen atoms and 28 isotropic hydrogens have converged to a conventional R factor of 0.042 (for **1**) and 0.073 (for **2**), respectively.

REFERENCES

1. (a) Fukazawa, Y.; Ogata, K.; Usui, S. *J. Am. Chem. Soc.* **1988**, *110*, 8692. (b) Okajima, T.; Wang, Z.-H.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, *30*, 1551. (c) Okajima, T.; Wang, Z.-H.; Fukazawa, Y. *Chemistry Lett.* **1991**, 37. (d) Fukazawa, Y.; Deyama, K.; Usui, S. *Tetrahedron Lett.* **1992**, *33*, 5803. (e) Wang, Z.-H.; Usui, S.; Fukazawa, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1239.
2. (a) ApSimon, J. W.; Craig, W. G.; Demarco, P. V.; Mathieson, D. W.; Saunders, L.; Whalley, W. B.*Tetrahedron,* **1967**, *23*, 2339. (b) ApSimon, J. W.; Craig, W. G.; Demarco, P. V.; Mathieson, D. W.; Saunders, L.; Whalley, W. B. *Tetrahedron,* **1967**, *23*, 2357. (c) ApSimon, J. W.; Craig, W. G.; Demarco, P. V.; Mathieson, D. W.; Saunders, L.; Whalley, W. B. *Tetrahedron,* **1967**, *23*, 2375. (d) ApSimon, J. W.; Demarco, P. V.; Mathieson, D. W.; Craig, W. G.; Karim, A.; Saunders, L.; Whalley, W. B. *Tetrahedron,* **1970**, *26*, 119. (e) ApSimon, J. W.; Beierbeck, H. *Can. J. Chem* . **1971**, *49*, 1328. (g) ApSimon, J. W.; Beierbeck, H.; Todd, D. K. *Can. J. Chem.* **1972**, *50*, 2351.
3. Zürcher, R.F. *Progr. NMR Spectrosc.* **1967**, *2*, 205.
4. Schneider, H. -J; Buchheit, U; Becker, N.; Schmidt, G.; Siehl, U. *J. Am. Chem. Soc.* **1985**, *107*, 7027.
5. Fukazawa, Y.; Hayashibara, T.; Yang, Y.; Usui, S. *Tetrahedron Lett.* **1995**, *36*, 3349.
6. Fukazawa, Y.; Ogata, K.; Usui, S. *J. Am. Chem. Soc.* **1988**, *110*, 8692.
7. Pople, J. A. *J. Chem. Phys.* **1962**, *37*, 60.
8. Lens, R. W.; Heeschen, J. P. *J. Polymer Sci.* **1961**, *51*, 247.
9. Hall, L. D. *Tetrahedron Lett.* **1964**, *23*, 1457.
10. Schaefer, T; Yonemoto,T. *Can. J. Chem.* **1964**, *42*, 2318.
11. (a) Turner, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 579. (b) Fujimoto, G. I. *J. Am. Chem. Soc.* **1951**, *73*, 1856.
12. Combe, M. G.; Henbest, H. B.; Jackson, W. R. *J. Chem. Soc. (C),* **1967**, 2468.
13. (a) Ruzicka, L.; Mhr, A. C. *Helv. Chim. Acta* **1944**, *27*, 503. (b) Tökés, L.; LaLonde, R. T.; Djerassi, C. *J. Chem. Soc. (C)* , **1967**, 1012.
14. (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**,*111*, 8551. (b) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566, 8576. (c) Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112* , 8293. (d) Schmitz, L. R.; Allinger, N. L. *J. Am. Chem. Soc.* **1990**, *112* , 8307. (e) Allinger, N. L.; Chen, K.; Rahman, M.; Pathiaseril, A. *J. Am. Chem. Soc.* **1991**, *113*, 4505. (f) Aped, P.; Allinger, N. L. *J. Am. Chem. Soc.* **1992**, *114*, 1. (g) Allinger, N. L.; Zhu, Z. S.; Chen, K. *J. Am. Chem. Soc.* **1992**, *114*, 6120. (h) Fox, P. C.; Bowen, J. P.; Allinger, N. L. *J. Am. Chem. Soc.* **1992**, *114*, 8536.
15. Buckingham, A. D. *Can. J. Chem.* **1960**, *38*, 300.
16. McConnell, H. M. *J. Chem. Phys.* **1957**, *27*, 266.
17. (a) Hall, L. D., Sanders, J. K. M., *J. Am. Chem. Soc.* **1980**, *102*, 5703. (b) Hall, L. D., Sanders, J. K. M. *J. Org. Chem.* **1981**, *46*, 1132.
18. (a) Blunt, J. W.; Stothers, J. B. *Org. Magn. Reson.* **1977**, *9*, 439. (b) Kalinowski,H.-O.; Berger, S.; Braun, S. "Carbon -13 NMR Spectroscopy"; St. Edmundsbury Press: U. K.,1988; pp. 129, 434. (c) Eggert, H.; Djerassi, C. *J. Org. Chem.* **1973**, *38*, 3788. (d) Gasic, M. J.; Djarmati, Z.; Pelletier, S. W. *J. Org. Chem.* **1976**, *41*, 1219. (e) Griffiths, D.V.,Wilcox, G. *J. Chem. Soc. Perkin Trans. 2* **1988**, 431.

(*Received in Japan* 10 *November* 1995; *accepted* 1 *December* 1995)